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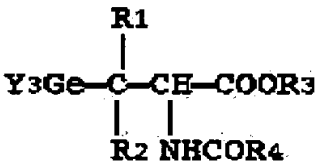
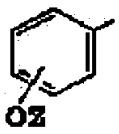
(54) ORGANOGERMANIUM COMPOUND

(57)Abstract:
PURPOSE: To obtain a new specific organogermanium compound having an amino acid structure introduced, and a variety of pharmacological actions, particularly an action to inhibit the Maillard reaction which is regarded as a cause of food deterioration.
CONSTITUTION: The new organogermanium compound of formula I [Y is a halogen, H; R1, R3 are H, a lower alkyl; R2 is a lower alkyl, carboxylakyl, a group of formula II (Z is H, acetyl); R4 is a lower alkyl or benzyloxy], for example, 1-(1-acetamide-1-carboxymethyl)ethylgermanium sesquioxide, which has a variety of pharmacological actions, particularly an action to inhibit the Maillard reaction which is reactions of amino compounds with reducing sugars as food components and is regarded as a cause of food deterioration: The compound is obtained by addition reaction of a germanium halide of the formula: HGeY3 to a compound of formula III in an organic solvent such as ethyl ether.



I



II

III

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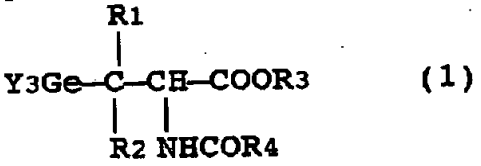
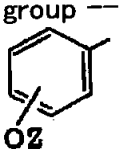
CLAIMS

[Claim(s)]
[Claim 1] Formula. [Formula 1]

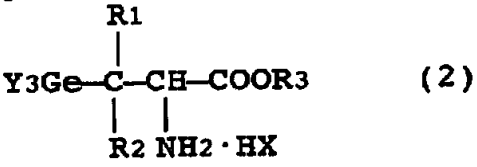


(1)

the inside of a formula, and Y -- a halogen atom or a hydrogen atom -- R1 and R3 -- a hydrogen atom or a low-grade alkyl group -- R2 -- a low-grade alkyl group and carboxy alkyl group -- or . [Formula 2]

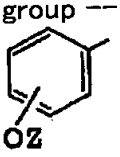


(Z expresses a hydrogen atom or an acetyl group) -- R4 -- a low-grade alkyl group or a benzyloxy machine -- respectively -- expressing -- the organic germanium compound characterized by what is expressed
[Claim 2] Formula. [Formula 3]

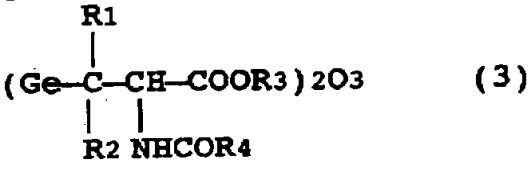


(2)

the inside of a formula, and Y -- a halogen atom or a hydrogen atom -- R1 and R3 -- a hydrogen atom or a low-grade alkyl group -- R2 -- a low-grade alkyl group and carboxy alkyl group -- or . [Formula 4]

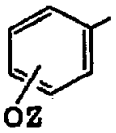


(Z expresses a hydrogen atom or an acetyl group) -- X -- halogen **** -- respectively -- expressing -- the organic germanium compound characterized by what is expressed
[Claim 3] Formula. [Formula 5]



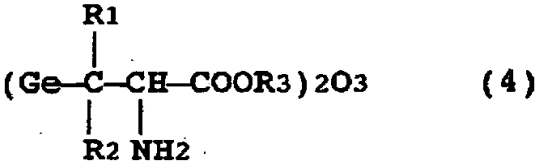
(3)

the inside of a formula, and R1 and R3 -- a hydrogen atom or a low-grade alkyl group -- R2 -- a low-grade alkyl group and carboxy alkyl group -- or . [Formula 6]



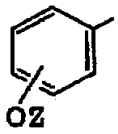
(Z expresses a hydrogen atom or an acetyl group) -- R4 -- a low-grade alkyl group or a benzyloxy machine -- respectively -- expressing -- the organic germanium compound characterized by what is expressed

[Claim 4] Formula. [Formula 7]



(4)

the inside of a formula, and R1 and R3 -- a hydrogen atom or a low-grade alkyl group -- R2 -- a low-grade alkyl group and carboxy alkyl group -- or . [Formula 8]



(Z expresses a hydrogen atom or an acetyl group) -- respectively -- expressing -- the organic germanium compound characterized by what is expressed

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[Translation done.]

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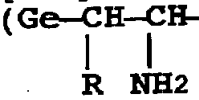
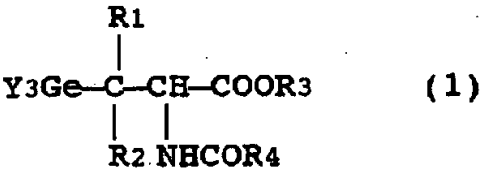
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] this invention relates to an organic germanium compound.
[0002]
[Description of the Prior Art] About the germanium germanium which is a carbonaceous homolog, it is observed also from the field of every direction especially medicine, or pharmacy as recent years come and the research on the organic compound and an announcement of the result come to be made actively. For example, about the KARUBOKISHIECHIRU germanium sesquioxide (JP,46-2498,B) which is the organic germanium compound which the propionic-acid derivative and oxygen atom of germanium combined at a rate of 2:3, it is reported that an interferon induction operation, antitumor action, etc. are shown just like [of a blood-pressure descent operation of a natural hypertension rat or not only a mitigation operation of amyloid change but a macrophage or a spontaneous killer cell] activation, and, also clinically, it is tried.
[0003] Since [2(germanium-CH2-CH2-COOH) O3] it is expressed with the becoming chemical formula, if it **, and the above-mentioned KARUBOKISHIECHIRU germanium sesquioxide can introduce the amino group into the alpha position of carboxyl group-COOH in the above-mentioned chemical formula fundamentally, such a compound can be considered to be the so-called kind of amino acid.
[0004] It is known well that it is the general term of a compound expressed with the becoming chemical formula, and the above-mentioned amino acid is what exists in all the living world where a life process is seen as a living body's indispensable constituent R-CH(NH2) COOH fundamentally. And not only in the point which amino acid combines the importance of amino acid and forms protein but in in the living body, amino acid is metabolized variously and is also in the point which serves as a precursor of other important matter for the living body. Therefore, if the above-mentioned amino acid structure can be introduced as the substructure to the aforementioned KARUBOKISHIECHIRU germanium sesquioxide by which it is known that the medicinal action which was already excellent is shown, it is fully expected that this organic germanium compound is what shows new usefulness.
[0005] On the other hand, it is in JP,02-62885,A. [Formula 9]

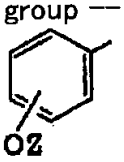


(R expresses a hydrogen atom, a low-grade alkyl group, or a phenyl group) etc. -- although the organic germanium compound which has an amino group in a side chain is indicated, if organic germanium compounds other than what introduced into the official report concerned the amino acid structure currently indicated substantially are compoundable, it is expected that those compounds are what shows still newer usefulness
[0006]
[Means for Solving the Problem] this invention was made in view of the conventional technology mentioned above, and the first organic germanium compound of this invention is a formula. [Formula 10]

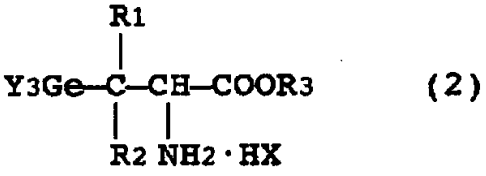


(1)

the inside of a formula, and Y -- a halogen atom or a hydrogen atom -- R1 and R3 -- a hydrogen atom or a low-grade alkyl group -- R2 -- a low-grade alkyl group and carboxy alkyl group -- or . [Formula 11]

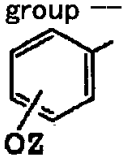


(Z expresses a hydrogen atom or an acetyl group) -- R4 -- a low-grade alkyl group or a benzyloxy machine -- respectively -- expressing -- what is characterized by what is expressed -- it is -- the second organic germanium compound of this invention -- a formula [Formula 12]



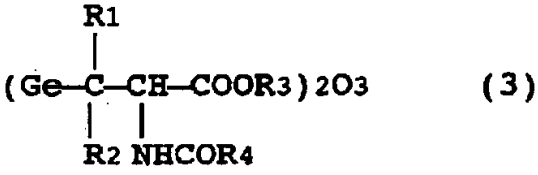
(2)

the inside of a formula, and Y -- a halogen atom or a hydrogen atom -- R1 and R3 -- a hydrogen atom or a low-grade alkyl group -- R2 -- a low-grade alkyl group and carboxy alkyl group -- or . [Formula 13]



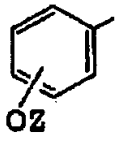
(Z expresses a hydrogen atom or an acetyl group) -- X -- halogen **** -- respectively -- expressing -- it is characterized by what is expressed

[0007] Moreover, the third organic germanium compound of this invention is a formula. [Formula 14]

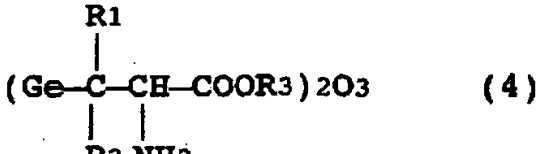


(3)

the inside of a formula, and R1 and R3 -- a hydrogen atom or a low-grade alkyl group -- R2 -- a low-grade alkyl group and carboxy alkyl group -- or . [Formula 15]

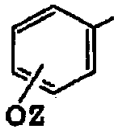


(Z expresses a hydrogen atom or an acetyl group) -- R4 -- a low-grade alkyl group or a benzyloxy machine -- respectively -- expressing -- what is characterized by what is expressed -- it is -- further -- the fourth organic germanium compound of this invention -- a formula [Formula 16]



(4)

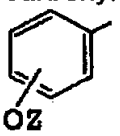
the inside of a formula, and R1 and R3 -- a hydrogen atom or a low-grade alkyl group -- R2 -- a low-grade alkyl group and carboxy alkyl group -- or . [Formula 17]



(Z expresses a hydrogen atom or an acetyl group) -- respectively -- expressing -- it is characterized by what is expressed

[0008] this invention is explained in detail below.

[0009] First, while the 1st organic germanium compound of this invention is expressed with the above-mentioned formula (1), and makes the propionic-acid derivative of germanium basic structure and three substituents Y combine with a germanium atom, two substituents R1 and R2 have combined [the amino group protected by protective groups, such as an acetyl group and a benzyloxycarbonyl machine, by the alpha position in propionic-acid structure] with beta grade again, and the oxygen functional group of a propionic acid has become COOR3 further. the low-grade alkyl group by which Y in a formula (1) is constituted here and R1 and R3 are constituted from 1 or about five carbon, such as a hydrogen atom or a methyl group, an ethyl group, n-propyl group, and an iso-propyl group, in a halogen atom or a hydrogen atom -- carboxy alkyl groups, such as the low-grade alkyl group as R1 with R2 [same], and a carboxymethyl machine, -- or . [Formula 18]



It means, respectively (Z expresses a hydrogen atom or an acetyl group).

[0010] Moreover, in the compound which is expressed with the above-mentioned formula (2) and is expressed with the above-mentioned formula (1), the second organic germanium compound of this invention is the same as the compound expressed with a formula (1), if the amino group protected by protective groups, such as an acetyl group, removes the point used as the salt of the hydrogen halide HX (X expresses a halogen atom).

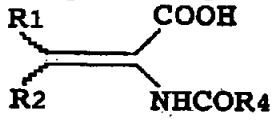
[0011] On the other hand, the third organic germanium compound of this invention is expressed with a formula (3), and although this compound differs from the compound expressed with the above-mentioned formula (1) and a formula (2) with the point which the propionic-acid derivative and oxygen atom of germanium combine at a rate of 2:3, it is the same as the compound fundamentally expressed with a formula (1) except it.

[0012] In addition, the compound expressed with the formula (1), formula (2), and formula (3) which gave [above-mentioned] explanation has very high usefulness as intermediate field at the time of compounding the fourth organic germanium compound of this invention explained below.

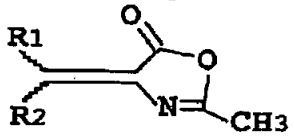
[0013] It ** and the final purpose compound of this invention is equivalent to that from which protective groups, such as an acetyl group which had protected the amino group in the compound which is expressed with the above-mentioned formula (4) and is expressed with the above-mentioned formula (3), were removed. namely, -- an alpha position [in / propionic-acid structure / this compound makes the propionic-acid derivative of germanium basic structure (however, the oxygen functional group is changed into COOR3), and] -- the amino group -- moreover, while substituents R1 and R2 combine with beta grade, 2:3 comes out comparatively and the aforementioned basic structure and an oxygen atom join together

[0014] About the above-mentioned compound (4), since it is the thing of the structure which did not exist in the former, it is expected enough that new usefulness is shown. Then, in order to check the usefulness of the compound of the above-mentioned this invention, it was the reaction of the amino compound and reducing sugar which are food constituents, and when the depressor effect of the Maillard reaction made into the cause of degradation of food was

examined, the above-mentioned compound (4) suppressed the Maillard reaction effectively by low concentration.
[0015] The organic germanium compound of this invention which **(ed) and gave [above-mentioned] explanation can be manufactured by the manufacture method which is explained below.
[0016] That is, for a substituent R3, the substituent Y among this invention compounds expressed with the above-mentioned formula (1) is [the thing of a hydrogen atom] the unsaturated compound into which substituents R1 and R2 are introduced beforehand with a halogen atom. [Formula 19]

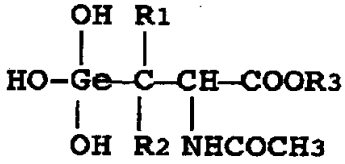


What is necessary is to be alike, to receive and just to make the halogenation compound expressed with a formula HGeY3 (Y expresses a halogen atom among a formula) add. In addition, this reaction advances in organic solvents, such as ethyl ether, or inorganic solvents, such as a hydrochloric acid.
[0017] Moreover, for a substituent R3, the substituent Y among this invention compounds expressed with the above-mentioned formula (1) is [the thing of a hydrogen atom] the azlactone object into which substituents R1 and R2 are introduced beforehand with a halogen. [Formula 20]

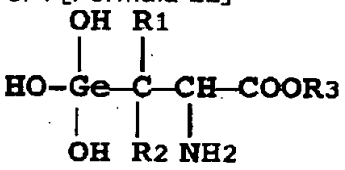


It understands by ****** and considers as the same unsaturated compound as the above (however, isolating is not indispensable), and even if it makes the halogenation compound expressed with a formula HGeY3 add to this unsaturated compound, it can obtain.
[0018] Furthermore, if Substituent Y can consider as the thing of a hydrogen atom among this invention compounds expressed with a formula (1) if it returns from the boron-hydride potassium KBH4, for example, the reactant of thionyl chloride and a lower alcohol is made to act, a substituent R3 can make germanium-Y combination in this invention compound expressed with the above-mentioned formula (1) the thing of a low-grade alkyl group among this invention compounds expressed with a formula (1). Of course, even if it uses together the conversion process by these reactions, it does not interfere. The same is said of other compounds of this invention mentioned later.
[0019] If the compound expressed with the above-mentioned formula (1) is processed by the hydrogen halide HY, although it can consider as the second compound of this invention expressed with the above-mentioned formula (2) If the compound (however, Substituent Y removes the thing of a hydrogen atom) expressed with a formula (1) is given to a adding-water decomposition reaction that this reaction should just treat the compound expressed with the above-mentioned formula (1) by hydrogen-halide solution, such as a hydrochloric acid Irrespective of the kind of R3, it can consider as the third compound of this invention expressed with the above-mentioned formula (3).
[0020] In addition, let the thing of a hydrogen atom be the third compound of this invention by which Substituent Y is expressed with a formula (3) by oxidizing this suitably among this invention compounds expressed with a formula (1).
[0021] And finally it can manufacture with the fourth compound of this invention expressed with the above-mentioned formula (4) by understanding the compound (however, Substituent Y removing the thing of a hydrogen atom) expressed with the above-mentioned formula (2) an added water part. In addition, the fourth compound of this invention expressed with a formula (4) can also be led from the compound expressed with a formula (1) or a formula (3).
[0022] **(ing), the spectrum data measured about the compound of this invention obtained as

mentioned above are supporting well that each compound of this invention is expressed with the above-mentioned formula. In addition, the compound of this invention expressed with the above-mentioned formula (3) and (4) is at underwater. [Formula 21]



or . [Formula 22]



** -- structure [like] is taken

[0023]

[Example] An example explains this invention still in detail below.

[0024] After adding 6.28g (0.04 mols) of synthetic a2-acetamide-3-methyl crotonic acids of this invention compound (however, R3=H) expressed with example 1 formula (1) into the 60ml concentrated hydrochloric acid and adding TORIKURORU germane 4.01g (0.05 mols), it agitated at the room temperature for 63 hours. When the crystal which deposited was filtered, it isolated preparatively and it recrystallized [hexane / the acetone and], 9.68g (it sets at a ceremony (1) and is the compound of Y=Cl and R1=R2=R4=CH3) (71.8% of yield) of 2-acetamide-3-methyl-3-(TORIKURORU gel mill) butanoic acids was obtained.

Melting point: 150 degree-C Anal(dec.).Calcd.:C. 24.94 ; H 3.59 ; N 4.15Found : C 24.93 ; H 3.58 ; N 4.07IR nu KBr/max cm-1:3330 (N-H), 1725 (C=O), 1605 (C=O), 405 1 (germanium-Cl) H-NMR (CDCl3+CD3OD) delta:1.40 (6H, s, C-(CH3) 2), 2.07 (3H, s, CO-CH3), 5.00 13 (1H, s, CH) C-NMR (Aceton-d6) delta:19.65 and 21.42 (2 (CH3)), 22.63 (N-CO-CH3), 51.29 (germanium-C), and 56.91 (CH), 171.16, 173.43 [(COO, CON changable)0025] b) Threonine 11.9g was dissolved in the solution containing 4.0g of sodium hydroxides, and ice-cooling, aqueous [containing 10.2g of acetic anhydrides and 4.0g of sodium hydroxides] was added simultaneously, and it stirred it as it was for 3 hours. N-acetyl threonine was obtained as colorless syrup almost quantitatively by adding 1Eq of diluted hydrochloric acid after a reaction end, adding ethanol to the colorless syrup obtained by distilling off a solvent by the evaporator, carrying out precipitation a ** exception, and condensing an ethanol layer.

[0026] Obtained N-acetyl threonine was dissolved in the acetic anhydride of an overlarge, and it considered as the azlactone object by stirring at a room temperature for 16 hours. Precipitation was filtered after the reaction end, by filling underwater [little by little a lot of] with filtrate, the azlactone was understood an added water part, the solvent was distilled off by the evaporator, and the 2-acetamino-2-butene acid was quantitatively obtained as yellow gum-like matter.

[0027] After dissolving 4.3g of obtained 2-acetamino-2-butene acids in chloroform and adding TORIKURORU germane 9.2g, it agitated at the room temperature for 19 hours. Distilling off of the solvent obtained quantitatively the 2-acetamide-3-(TORIKURORU gel mill) butanoic acid (it sets at a ceremony (1) and is the compound of Y=Cl, R1=R4=CH3, and R2=H) as yellow sirupy matter after the reaction end.

1 H-NMR (CD3OD) delta:1.33, 1.37 (3H, d CH3 each), 2.04 (3H, s, CH3CO), 2.5-2.9 (1H, m, germanium-CM), 4.90, and 4.94 (1H, d NOC-CH each) [0028] c) In addition, other compounds expressed with a formula (1) were able to be obtained by the method indicated to Above a and b, and the almost same method. The yield and the physical properties of a compound which were acquired are as illustrating to the following and Table 1.

[0029] 2-acetamide-3-(TORIKURORU gel mill) pentanoic acid (it sets at a ceremony (1) and is the compound of Y=Cl, R1=H, R2=CH2CH3, and R4=CH3)

yield: -- 73.7% melting point: -- 163-164 degree-CAnal.Calcd.:C 24.94 ; H 3.59 ; N 4.15Found : C 24.81 ; H 3.52 ; N 4.20IR nu KBr/max cm-1:3330 (N-H), 1720 (C=O) 1640 (C=O), 430 1 (Germanium-Cl) H-NMR (Aceton-d6) Delta:1.17 (3H, T, CH3), 1.86 (1H, ddq, CH3-C-Ha) and 2.00 (1H, ddq, CH3-C-Hb), 2.08 (3H, s, CO-CH3) and 2.90 (1H, ddd, germanium-CH), 5.10 13 (1H, d, CH-CO) C-NMR (Aceton-d6) delta:13.32 (CH3), 19.99 (CH2), 22.31 (CO-CH3), 52.66 (germanium-C), and 53.32 (CH), 171.59, and 172.07 (COO, CON changable) [0030] 2-acetamide-4-methyl-3-(TORIKURORU gel mill) pentanoic acid (it sets at a ceremony (1) and is the compound of Y=Cl, R1=H, R2=CH (CH3)2, and R4=CH3)
yield: -- 60.1% melting point: -- 119-120 degree-CAnal.Calcd.:C 27.36 ; H 4.02 ; N 3.99Found : C 27.39 ; H 4.01 ; N 3.99IR nu KBr/max cm-1:1720 (C=O), 1620 (C=O) 415 1 (Germanium-Cl) H-NMR (CDCl3, CD3OD) Delta:1.19 and 1.23 (3HX2, D, 2 (CH3)), 2.07 (3H, s, CO-CH3), 2.33 (1H, oct, 2(CH3)-CH), 2.93 (1H, dd, germanium-CH), and 5.16 (1H, d, CH-CO) [0031] 2-acetamide-3-methyl-3-(TORIKURORU gel mill) pentanoic acid (it sets at a ceremony (1) and is the compound of Y=Cl, R1=CH3, R2=CH2CH3, and R4=CH3)
Yield: 59.4% (mixture of a diastereomer)
Melting point: 163-164 degree-CAnal.Calcd.:C 27.36 ; H 4.02 ; N 3.99Found : C 27.05 ; H 4.19 ; N 3.88IR nu KBr/max cm-1:3360 (N-H), 1725, 1660 (C=O), 410, 395 1 (germanium-Cl) H-NMR (CDCl3+CD3OD) delta:1.12 and 1.17 (3Hx2, tx2, germanium-C-C-CH3), 1. 37, 1.42 (3Hx2, sx2, germanium-C-CH3), 1.89 (2Hx2, q, germanium-C-CH2), 2.10 (3Hx2, s, CO-CH3), and 5.18 (1Hx2, s, CH-CO) [0032] 2-(KARUBO benzyloxyamino)- 3-(TORIKURORU gel mill) pentane 2 acid (it sets at a ceremony (1) and they are Y=Cl, R1=H, R2=CH2COOH, and the compound of R4=OCH2C6H5)
Yield: 75.1% (mixture of a diastereomer)
Melting point: 123 degree-C IR (dec.) nu . KBr/max cm-1:1708(C=O) 1 H-NMR (CD3OD) delta:2.80-3.20 (3H, GeCH-CH2), 4.87 (1H, CH-N) and 5.21 (2H, CH2-ph), 7.44 13 (5H, pH) C-NMR (CD3OD) delta:31.35 and 32.64 (germanium-CH2-CH2), 54.50, 55.27 (germanium-CH2-CH), 68.33 (CH2-pH), 129.1, 129.3, and 129.7 (pH) [0033] d) After dissolving 9.2g (it sets at a ceremony (1) and is the compound of Y=Cl, R1=R4=CH3, and R2=H) of 2-acetamide-3-(TORIKURORU gel mill) butanoic acids in potassium-hydroxide solution and being referred to as pH 7, boron-hydride potassium 5.66g was added and it stirred for 30 minutes at the room temperature. After the reaction end, diluted hydrochloric acid was added, it was referred to as pH 1, precipitation was filtered, and filtrate was extracted with ethyl-acetate ester. 4.7g (it sets at a ceremony (1) and is the compound of Y=H, R1=R4=CH3, and R2=H) of 2-acetamide-3-gel mill butanoic acids was obtained as colorless quality of a powdered material by condensing an ethyl-acetate ester layer after dryness with sulfuric-anhydride magnesium.
Yield: 71.3% (mixture of a diastereomer)
Melting point: 99-105 degree-CAnal.Calcd.:C 32.79 ; H 5.96 ; N 6.37Found : C 32.91 ; H 6.10 ; N 6.22IR nu KBr/max cm-1:2080 (GeH), 1710 (CO), 1610 1 (C-N) H-NMR (CD3OD) Delta:1.19 (3H, D, CH3), 1.8-2.1 (1H, m, germanium-CH), 1.97, 1.99 (each s [3H and], CH3CO), 3.58, 3.61 (3H, d GeH3 each), 4.48, and 4.57 (1H, d CH-NAc each) [0034]
[Table 1]

Y	R_1	R_2	R_3	R_4	収率
Cl	CH_2CH_3	H	H	CH_3	73.7
Cl	$CH_2CH_2CH_3$	H	H	CH_3	77.0
Cl	H	p-OH-C_6H_5	H	CH_3	87.2
Cl	CH_3	CH_3	CH_2CH_3	CH_3	80

[0035] 16.86g (it sets at a ceremony (1) and is the compound of Y=Cl, R1=H, and R2=CH2CH3) (0.05 mols) of synthetic a2-acetamide-3-(TORIKURORU gel mill) pentanoic acids of this invention compound (however, R3=H) expressed with example 2 formula (2) was dissolved in 40ml water, 40ml of concentrated hydrochloric acids was added, and heating

reflux was carried out for 2.5 hours. the solvent was distilled off, the crystal which deposited was dissolved in 100ml water, and hydrogen chloride gas was passed for about 1 hour until generation of heat stopped however -- By separating the crystal which deposited after cooling, the 2-amino-3-(TORIKURORU gel mill) pentanoic-acid hydrochloride (it sets at a ceremony (2) and is the compound of X=Y=Cl, R1=H, and R2=CH2CH3) was considered as the white crystal, and was obtained 9.96g.
yield: -- 60.1% melting point: -- 180-181degree-C(dec.) Anal.Calcd.:C 18.11 ; H 3.34 ; N 4.22Found : C 17.92 ; H 3.31 ; N 4.02IR nu KBr/max cm-1:1750 (C=O), 420 1 (germanium-Cl) H-NMR (CD3OD) delta:1.17 (3H, t, CH3), 1.73, 1, and 94 (1Hx2, mx2, CH3-CH2), 2.62 (1H, m, germanium-CH), 4.56 13 (1H, br, CH-N) C-NMR (CD3OD) delta:13.46 (CH3), 18.85 (CH2), and 54.12 (CH-N) [0036] b) In addition, other compounds expressed with a formula (2) were able to be obtained by the method indicated to Above a, and the almost same method. The yield and the physical properties of a compound which were acquired are as illustrating to the following and Table 2.
[0037] 2-amino-4-methyl-3-(TORIKURORU gel mill) pentanoic-acid hydrochloride (it sets at a ceremony (2) and is the compound of X=Y=Cl, R1=H, and R2=CH (CH3)2)
yield: -- 61.0% melting point: -- 165-166degree-C(dec.) Anal.Calcd.:C 20.85 ; H 3.79 ; N 4.05Found : C 20.80 ; H 3.90 ; N 4.35IR nu KBr/max cm-1:1730 (C=O), 420 1 (germanium-Cl) H-NMR (CD3 OD+CDCl3) delta:1.19 and 1.29 (6H, dx2, 2 (CH3)), 2.47 (1H, oct, 2(CH3)-CH) and 3.07 (1H, dd, germanium-CH), 4.60 13 (1H, d, CH-CO) C-NMR (CD3OD) delta:21.02 and 23.71 (2 (CH3)), 27.63 (2(CH3)-CH), 50.86 (germanium-CH), 53.48 (N-CH), and 170.46 (CO)
[0038] 2-amino-3-methyl-3-(TORIKURORU gel mill) butanoic-acid hydrochloride (it sets at a ceremony (2) and is the compound of X=Y=Cl and R1=R2=CH3)
yield: -- 88.1% melting point: -- 149-150degree-C(dec.) Anal.Calcd.:C 18.11 ; H 3.34 ; N 4.22Found : C 18.12 ; H 3.20 ; N 4.56IR nu KBr/max cm-1:1750 (C=O), 430, 405 1 (germanium-Cl) H-NMR (CD3 OD+CDCl3) delta:1.44 (3H, s, CH3), 1.65 (3H, s, CH3), and 4.42 (1H, s, CH-CO) [0039] 2-amino-3-methyl-3-(TORIKURORU gel mill) pentanoic-acid hydrochloride (it sets at a ceremony (2) and is the compound of X=Y=Cl, R1=CH3, and R2=CH2CH3)
Yield: 61.0% (mixture of a diastereomer)
Melting point: 150degree-C(dec.) Anal.Calcd.:C. 20.85 ; H 3.79 ; N 4.05Found : C 20.55 ; H 3.98 ; N 4.47IR nu KBr/max cm-1:1765 (C=O), 420, 400 1 (germanium-Cl) H-NMR (CD3OD) delta:1.13 (3Hx2, t, germanium-C-C-CH3), 1.33, 1.57 (3Hx2, sx2, germanium-C-CH3), 1.67-2.57 (2Hx2, m, germanium-C-CH2), 4.42, and 4.52 (1Hx2, sx2, CH-CO) [0040] 2-amino-3-(TORIKURORU gel mill) pentane diacid hydrobromate (it sets at a ceremony (2) and is the compound of X=Br, Y=Cl, R1=H, and R2=CH2COOH)
Melting point: 153-degree-C(dec.) IR nu KBr/max cm-1:1723 1 (C=O) H-NMR (CD3OD) delta:2.80-3.10 (3H, germanium-CH-CH2), 4.68, and 4.78 (1H, CH-N) [0041]
[Table 2]

X	Y	R_1	R_2	R_3	収率
Cl	Cl	CH_2CH_3	H	H	60.1
Cl	Cl	$CH_2CH_2CH_3$	H	H	69.7
Cl	Cl	H	p-OH-C_6H_5	H	63.5
Cl	Cl	CH_3	CH_3	CH_2CH_3	66.3

[0042] The synthetic a2-acetamide-4-methyl-3-(TORIKURORU gel mill) pentanoic acid of this invention compound (however, R3=CH2CH3) expressed with example 3 formula (3) (setting at a ceremony (1)) 10.53g (0.03 mols) of compounds of Y=Cl, R1=H, R2=CH (CH3)2, R3=H, and R4=CH3 was dissolved in 50ml ethanol, thionyl chloride 3.93g (0.033 mols) was added, and heating reflux was carried out for 1 hour. Since the mixture of a crystal and oily matter was obtained when the solvent was distilled off, when the ether washed this, insoluble matter was filtered and concentration hardening by drying of the filtrate was carried out, the mixture of a crystal and oily matter was obtained. This is dissolved in 300ml water and it stirs for 3 hours, and insoluble matter is filtered, a dechlorination is carried out to an anion

exchange resin (IRA-45, AcOH) through filtrate, and concentration hardening by drying of the filtrate is carried out, 4.02g (it sets at a ceremony (3) and is the compound of R1=H, R2=CH (CH3)2, and R4=CH3) of 1-(1-acetamide-1-ethoxy carbonylmethyl)-2-methylpropyl germanium sesquioxide was obtained as powder of fine yellow.
yield: -- 56.5% melting point: -- 160degree-C(dec.) Anal.Calcd.:C 40.46 ; H 6.11 ; N 4.72Found : C 40.18 ; H 5.93 ; N 4.51IR nu KBr/max cm-1:1735 and 1660 (C=O), 875 1 (germanium-O) H-NMR (D2O) delta:1.05 (6H, m, 2 (CH3)), 1.28 (3H, t, O-C-CH3) and 2.06 (3H, s, CO-CH3), 2.07 (1H, m, 2(CH3)-CH), 2.11 (1H, m, germanium-CH), 4.23 (2H, m, O-CH2), and 4.97 (1H, d, CH-CO) [0043] b) In addition, other compounds expressed with a formula (3) were able to be obtained by the method indicated to Above a, and the almost same method. The yield and the physical properties of a compound which were acquired are as illustrating to the following and Table 3.
[0044] 2-acetamide-2-(ethoxycarbonyl)-1 and 1-dimethyl-ethyl germanium sesquioxide (it sets at a ceremony (3) and is the compound of R1=R2=R4=CH3)
yield: -- 59.3% melting point: -- 170degree-C(dec.) Anal.Calcd.:C 38.22 ; H 5.70 ; N 4.95Found : C 37.99 ; H 5.61 ; N 4.79IR nu KBr/max cm-1:1735 and 1660 (C=O), 860 1 (germanium-O) H-NMR (D2O) delta:1.22 and 1.25 (3Hx2, sx2, germanium-C -(CH3) 2), 1.30 (3H, t, CH2-CH3), 2.11 (3H, s, CO-CH3), 4.27 (2H, br, CH2), and 4.80 (1H, s, CO-CH) [0045] 1-(1-acetamide-1-ethoxy carbonylmethyl)-1-methylpropyl germanium sesquioxide (it sets at a ceremony (3) and is the compound of R1=R4=CH3 and R2=CH2CH3)
Yield: 32.2% (mixture of a diastereomer)
Melting point: 175 degree-C(dec.) Anal.Calcd.:C40.46. ; H 6.11 ; N 4.72Found : C40.21 ; H 5.92 ; N 4.55IR nu KBr/max cm-1:1730 and 1660 (C=O), 860 1 (germanium-O) H-NMR (CH3OD) : [1.08 (3Hx2, br, germanium-C-C-CH3),] 1.28 (6Hx2, br, germanium-C-CH3, O-C-CH3), 1.73 (2Hx2, br, germanium-C-CH2), 2.04 (3Hx2, br, CO-CH3), 4.19 (2Hx2, br, O-CH2), 4.86 [(1Hx2, br, CO-CH)0046]
[Table 3]

R_1	R_2	R_3	R_4	収率
CH_2CH_3	H	CH_2CH_3	CH_3	57.0
$CH_2CH_2CH_3$	H	CH_2CH_3	CH_3	61.3
H	CH_2COOH	CH_2CH_3	CH_3	58.2
H	p-OH-C_6H_3	CH_2CH_3	CH_3	60.9

[0047] The synthetic a2-acetamide-3-gel mill butanoic acid (it sets at a ceremony (1) and is the compound of Y=H, R1=H, and R2=R4=CH3) of this invention compound (however, R3=H) expressed with example 4 formula (3) was dissolved in the mixed solvent of a methanol and dichloromethane, 3.94g of meta-crawl perbenzoic acids was added, and it stirred for 30 minutes at the room temperature. 1.0g (it sets at a ceremony (3) and is the compound of R1=H and R2=R4=CH3) of 1-(1-acetamide-1-carboxymethyl) ethyl germanium sesquioxide was obtained as colorless powder by separating the precipitation which deposited after a reaction end and washing with the ether.
Yield: 60.1% (mixture of a diastereomer)
Melting point: 257degree-C(dec.) Anal.Calcd.:C. 38.22 ; H 5.70 ; N 4.95Found : C 38.13 ; H 5.52 ; N 4.01IR nu KBr/max cm-1:3700-2900 (NH, OH), 1720, 1650 (C=O), 880, 820 1 (germanium-O) H-NMR (D2O) delta: Diastereomer a 1.15 (3H, d, CH3), 2.07 (3H, s, CH3-CO) and 2.26 (1H, dq, germanium-CH), 4.82 diastereomer b (1H, d, N-CH) 1.26 (3H, d, CH3), 2.06 (3H, s, CH3-CO), 2.22 (1H, dq, germanium-CH), and 4.44 (1H, d, N-CH) [0048] b) After having dissolved 1.88g (it sets at a ceremony (1) and is the compound of Y=Cl, R1=H, an R2= parlor SETOKISHI phenyl, R3=H, and R4=CH3) of 2-acetamide-3-(parlor SETOKISHI phenyl)-3-TORIKURORU gel mill propanoic acid in water, adding 1.78g of sodium hydrogencarbonates and stirring at a room temperature for 20 hours, 4.4ml of 1-N sodium-hydroxide solution was added, and it stirred for further 2 After the reaction end, diluted hydrochloric acid was added, it was referred to as pH 7, and the methanol was added and filtered. Filtrate was condensed,

operation of separating the precipitation which added the methanol to the residue and deposited was performed twice, and 0.82g yellow powder was obtained. It is 2 by dissolving this in distilled water and condensing a water layer after stirring cation-exchange-resin Amberlite IR120B (tradename) [H+ type] and overnight. - 700mg (it sets at a ceremony (3) and they are R1=H, an R2= PARAHAIDOROKISHI phenyl, and the compound of R4=CH3) of acetamide-2-carboxy-1-PARAHAIDOROKISHIFENIRUECHIRU germanium sesquioxide was obtained as powder of fine yellow.
Yield: 58.9% (mixture of a diastereomer)
Melting point: 300degree-C<(dec.) Anal.Calcd.:C. 38.22 ; H 5.70 ; N 4.95Found : C 38.00 ; H 5.51 ; N 4.72IR nu KBr/max cm-1:3600-2500 (NH, OH), 1710, 1640 (C=O), 875, 840 1 (germanium-O) H-NMR (D2O) delta:1.87 (3H, s, CH3-CO), 3.55 (1H, d, germanium-CH), 4.98 (1H, d, N-CH), 6.87 (ortho position of 2H, d, and OH), and 7.04 (meta position of 2H, d, and OH) [0049] c) 1-(1-acetamide-1-ethoxy carbonylmethyl)-2-methylpropyl germanium sesquioxide (it sets at ceremony (3) and is compound of R1=H, R2=CH (CH3)2, R3=CH3CH2, and R4=CH3) 2.97g (0.005 mols) was suspended in 80ml water, 0.44g (0.011 mols) of sodium hydroxides was added, and it stirred for 17 hours. After filtering and carrying out ** sodium to cation-exchange-resin Amberlite IR120B (tradename) [H+ type] through filtrate after a reaction end, concentration hardening by drying of the filtrate is carried out, 1.36g (it sets at a ceremony (3) and is the compound of R1=H, R2=CH (CH3)2, and R4=CH3) of 1-(1-acetamide-1-carboxymethyl)-2-methylpropyl germanium sesquioxide was obtained as powder of fine yellow.
yield: -- 50.6% melting point: -- 207 degree-C(dec.) Anal.Calcd.:C35.75 ; H5.25 ; N5.21Found : C35.56 ; H5.06 ; N5.20IR nu KBr/max cm-1:1740 and 1665 (C=O), 875(germanium-O) 1 H-NMR (D2 O+NaOD) delta:1.06 and 1.08 (6H, d, 2 (CH3)), 2.06 (3H, s, CO-CH3), 1.83-2.33 (2H, m, CH-CH), and 4.56 (1H, d, CO-CH) [0050] d) In addition, other compounds expressed with a formula (3) were able to be obtained by the method indicated to Above a and b or c, and the almost same method. The yield and the physical properties of a compound which were acquired are as illustrating to the following and Table 4.
[0051] The 2-acetamide-2-carboxy -1, 1-JIMECHIRUECHIRU germanium sesquioxide (it sets at a ceremony (3) and is the compound of R1=R2=CH3 and R4=CH3)
yield: -- 82.5% melting point: -- 210 degree-C(dec.) Anal.Calcd.:C33.00 ; H 4.75 ; N5.50Found : C32.71 ; H 4.61 ; N 5.27IR nu KBr/max cm-1:1720 and 1650 (C=O), 880(germanium-O) 1 H-NMR (D2O) delta:1.08 (3H, s, CH3), 1.17 (3H, s, CH3) 2.11 (3H, s, CO-CH3), 4.62 13 (1H, s, CO-CH) C-NMR (D2O, NaOD) delta:22.64 and 23.71 (2 (CH3)), 24.98 (CO-CH3), 38.54 (germanium-C), and 64.28 (CH), 176.68, and 180.06 (COO, CON changable) [0052] 1-(1-acetamide-1-carboxymethyl)-1-methylpropyl germanium sesquioxide (it sets at a ceremony (3) and is the compound of R1=CH3, R2=CH2CH3, and R4=CH3)
Yield: 71.7% (mixture of a diastereomer)
Melting point: 184 degree-C(dec.) Anal.Calcd.:C35.75. ; H5.25 ; N5.21Found : C35.63 ; H5.19 ; N 5.19IR nu KBr/max cm-1:1720 and 1660 (C=O), 870(germanium-O) 1 H-NMR (D2 O+NaOD) delta : Diastereomer a 1.01 (3H, t, CH3), 1.36 (1H, dq, CH3-CHa) and 1.67 (1H dq, CH3-CHb), 1.09 (3H, s, germanium-C-CH3) and 2.10 (3H, s, CO-CH3), The 4.82 diastereomer (1H, s, CO-CH) b0.99 (3H, t, CH3), 1.50 (2H, dq, CH3-CH2) and 1.15 (3H, s, germanium-C-CH3), 2.10 (3H, s, CO-CH3), 4.65 13 (1H, s, CO-CH) C-NMR (D2O, NaOD) delta: Diastereomer a 13.24 (germanium-C-CH3), 20.73 (CH3), 24.78 (CO-CH3), and 30.77 (CH2), 46.90 (germanium-C), 58.61 diastereomer b (CH-CO) 12.96 (germanium-C-CH3), 21.36 (CH3), 24.83 (CO-CH3), 27.94 (CH2), 47.33 (germanium-C), 62.41 a (CH-CO), b 177.10, 177.13, 180.19, and 180.67 (COO, CON changable) [0053]

R_1	R_2	R_3	R_4	収率
CH_2CH_3	H	H	CH_3	96.9
$CH_2CH_2CH_3$	H	H	CH_3	78.2
H	CH_2COOH	H	CH_3	83.1

[0054] Synthetic a2-amino of this invention compound (however, R3=H) expressed with example 5 formula (4) -3 -(TORIKURORO gel mill)- Pentanoic-acid hydrochloride (in a formula (2)) 8.29g (0.025 mols) of compounds of X=Y=Cl, R1=H, and R2=CH2CH3 is dissolved in 100ml water. After making it stick to cation-exchange-resin Amberlite IR120B (tradename) [H+ type] and rinsing, it is eluted with 2-N aqueous ammonia, and filtrate is hardened by drying. 1 -(1-amino-1-carboxymethyl)- 4.62g (it sets at a ceremony (4) and is the compound of R1=H and R2=CH<SUB>2CH3) of propyl germanium sesquioxide was obtained as powder of fine yellow.
yield: -- 86.9% melting point: -- 206degree-C(dec.) Anal.Calcd.:C 28.23 ; H 4.74 ; N 6.5Found : C 28.06 ; H 4.59 ; N 6.44IR nu KBr/max cm-1:1630 (C=O), 870(germanium-O) 1 H-NMR (D2O) delta:1.09 (3H, t, CH3), 1.51 (1H, ddq, CH3-CHa) and 1.74 (1H, ddq, CH3-CHb), 2.09 (1H, ddd, germanium-CH), 4.19 13 (1H, d, CO-CH) C-NMR (D2O) delta:15.67 (CH3), 19.82 (CH3-CH2) 40.51 (germanium-CH), 57.70 (CH-N), and 176.20 (CO) [0055] b) The concentrated hydrochloric acid was added to 969mg (it sets at a ceremony (1) and they are Y=Cl, R1=H, an R2= parlor SETOKISHI phenyl, and the compound of R4=CH3) of 2-acetamide-3-(parlor SETOKISHI phenyl)-3-TORIKURORU gel mill propanoic acid, and it stirred for two days at the room temperature. After the reaction end, underwater [a lot of] was filled with contents, and the impurity was filtered. It is 2 by dissolving the residue which condensed and obtained filtrate in distilled water, making it stick to cation-exchange-resin Amberlite IR120B (tradename) [H+ type], being eluted with aqueous ammonia 5%, and condensing an eluate. -200mg (it sets at a ceremony (4) and is the compound of an R1=H and R2= PARAHAIDOROKISHI phenyl) of amino-2-carboxy-1-PARAHAIDOROKISHIFENIRUECHIRU germanium sesquioxide was obtained as powder of fine yellow.
Yield: 46.2% (mixture of a diastereomer)
Melting point: 300degree-C>(dec.) Anal.Calcd.:C. 28.23 ; H 4.74 ; N 6.5Found : C 28.00 ; H 4.56 ; N 6.32IR nu KBr/max cm-1:3700-2200 (NH3+), 1630 (NH3+), 1605 (C=O), 885, 845 1 (germanium-O) H-NMR (D2O) delta:3.38 (1H, d, germanium-CH), 4.33 (1H, d, CO-CH), 6.87 (ortho position of 2H, d, and OH), and 7.14 (meta position of 2H, d, and OH) [0056] c) 1-(1-acetamide-1-carboxymethyl) ethyl germanium sesquioxide (it sets at ceremony (3) and is compound of R1=H, R2=CH3, and R4=CH3) 200mg was dissolved in water, 0.2ml of concentrated hydrochloric acids was added further, and heating reflux was carried out for 18 hours. Reaction mixture was condensed after the reaction end, the obtained white crystal was again dissolved in water, the impurity was filtered, and it let filtrate pass to cation-exchange-resin Amberlite IR120B (tradename) [H+ type]. After fully rinsing, it was eluted with aqueous ammonia 5.6%, and 126mg (it sets at a ceremony (4) and is the compound of R1=H and R2=CH3) of 1-(1-amino-1-carboxymethyl) ethyl germanium sesquioxide was obtained as powder of an off-white by condensing an eluate.
yield: -- 76.3% melting point: -- 270degree-C(dec.) Anal.Calcd.:C 24.18 ; H 4.06 ; N 7.05Found : C 24.00 ; H 3.88 ; N 6.91IR nu KBr/max cm-1:3800-2500 (NH, OH), 1610 (C=O), 840, 790 (germanium-O) 1 H-NMR (D2O) delta: Diastereomer a 1.19 (3H, t, CH3), 2.19 (1H, dq, germanium-CH), 4.19 diastereomer b (1H d, CO-CH) 1.36 (3H, t, CH3), 2.09 (1H, dq, germanium-CH), and 3.86 (1H d, CO-CH) [0057] d) In addition, other compounds expressed with a formula (4) were able to be obtained by the method indicated to Above a and b or c, and the almost same method. The yield and the physical properties of a compound which were acquired are as illustrating to the following and Table 5.
[0058] 1-(1-amino-1-carboxymethyl)-2-methylpropyl germanium sesquioxide (it sets at a ceremony (4) and is the compound of R1=H and R2=CH (CH3)2)

yield: -- 71.0% melting point: -- 191degree-C(dec.) Anal.Calcd.:C 31.78 ; H 5.33 ; N 6.18Found : C 31.48 ; H 5.09 ; N 6.10IR nu KBr/max cm-1:1630 (C=O), 860 1 (germanium-O) H-NMR (D2O) delta:1.01 and 1.15 (6H, d, 2 (CH3)), 2.17 (1H, d sept, 2(CH3)-CH) and 2.29 (1H, dd, germanium-CH), 4.18 (1H, d, CH-CO) 13 C-NMR (D2O) delta:22.71, 25.84 (2 (CH3)), 27.80 (2 (CH3)-CH), 46.03 (germanium-CH), 56.89 (CH-N), and 177.13 (CO) [0059] 1-(1-amino-1-carboxymethyl)-1-methyl-ethyl germanium sesquioxide (it sets at a ceremony (4) and is the compound of R1=R2=CH3)
yield: -- 80.0% melting point: -- 190degree-C(dec.) Anal.Calcd.:C 28.23 ; H 4.74 ; N 6.58Found : C 28.04 ; H 4.64 ; N 6.56IR nu KBr/max cm-1:1640 (C=O), 850(germanium-O) 1 H-NMR (D2O) delta:1.53 (3H, s, CH3), 1.36 (3H, s, CH3), and 3.95 (1H, s, CH) [0060] 1-(1-amino-1-carboxymethyl)-1-methyl-propyl germanium sesquioxide (it sets at a ceremony (4) and is the compound of R1=CH3 and R2=CH2CH3)
Yield: 84.6% (mixture of a diastereomer)
Melting point: 195degree-C(dec.) Anal.Calcd.:C. 31.78 ; H 5.33 ; N 6.18Found : C 31.53 ; H 5.44 ; N 6.11IR nu KBr/max cm-1:1650 (C=O), 845 1 (germanium-O) H-NMR (D2O) delta:1.06 (3Hx2, t, germanium-C-C-CH3), 1.17, 1.38 (3Hx2, sx2, germanium-C-CH3), 1.30-2.27 (2Hx2, m, germanium-C-CH2), 4.00, 4.19 (1Hx2, sx2, CO-CH) [0061] 2 - Amino-2-carboxy-1-(carboxymethyl) ethyl germanium sesquioxide (it sets at a ceremony (4) and is the compound of R1=H and R2=CH2COOH)
Yield: 74.21% (mixture of a diastereomer)
Melting point: 345-degree-C(dec.) IR nu KBr/max. cm-1:1663 1 (C=O) H-NMR (D2O) delta:2.33-2.85 (3H, germanium-CH-CH3), 4.10 13 (1H, CH-N) C-NMR (D2O, dioxane) delta:31.22 and 31.44 (germanium-CH2-CH2), 34.29, 34.56 (ge-CH), 52.16, 57.19 (CH-N), 174.2, and 179.7 (C=O) [0062]
[Table 5]

R_1	R_2	R_3	収率
CH_2CH_3	H	H	86.9
$CH_2CH_2CH_3$	H	H	80.5
H	CH_3	CH_2CH_3	81.3
CH_3	CH_3	CH_2CH_3	84.2

[0063]
[Reference experiment] Manufacture undiluted solution N alpha-t-Boc-L-Lysine (50mM) of the prevention effect 1. sample solution of a Maillard reaction with this invention compound and the glucose (1M) were dissolved in 240ml of 50ml phosphate buffers, and it considered as the undiluted solution.
It dissolved in 30ml of control liquid undiluted solutions at 30ml of 50ml phosphate buffers, and considered as control liquid.
an organic germanium compound liquid organic germanium compound -- respectively -- 20 -- mM(s) were taken, it dissolved in the phosphate buffer of 50mM, and was referred to as 50ml, and 30 of ml of it were mixed with 30ml of undiluted solutions, and it considered as the organic germanium compound liquid of 10mM
[0064] 2. Each above-mentioned sample solution was mixed as a result of the examination of the prevention effect, it incubated under 40-degree C shaking conditions, the shell sample was extracted on 4, 8, and the 11th, respectively, and the absorbance in 297nm (absorption maximum) was measured. A result is shown in the following table 6.
[Table 6]

化合物			吸光度(297nm)		
R_1	R_2	R_3	4日目	8日目	11日目
H	CH_2CH_3	H	0.37	0.54	1.35
H	p-OH-C_6H_5	H	0.34	0.53	1.31
H	CH_3	H	0.39	0.55	1.26
H	$CH(CH_3)_2$	H	0.33	0.55	1.30
CH_3	CH_3	H	0.33	0.51	1.25
CH_3	CH_2CH_3	H	0.32	0.52	1.21
H	CH_2COOH	H	0.31	0.55	1.19
CH_2CH_3	H	H	0.33	0.53	1.15
H	CH_3	CH_2CH_3	0.30	0.47	1.08
CH_3	CH_3	CH_2CH_3	0.29	0.48	1.05
H	H	H	0.39	1.17	2.78
C_6H_5	H	H	0.41	1.26	2.55
コントロール			0.50	1.51	3.13

[Translation done.]

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(51)Int.Cl.[6]	識別記号	庁内整理番号	ＦＩ	技術表示箇所
C07F 7/30		D		

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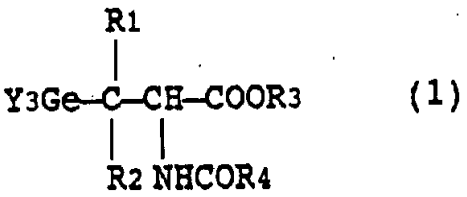
(54)【発明の名称】　有機ゲルマニウム化合物

(57)【要約】　(修正有)

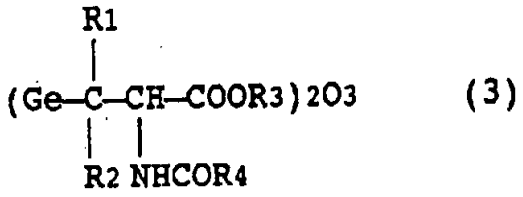
【目的】　アミノ酸構造を導入した有機ゲルマニウム化合物は公知であるが、当該公知化合物と異なるアミノ酸構造を導入した有機ゲルマニウム化合物を提供する。

【構成】　本有機ゲルマニウム化合物は一般式1



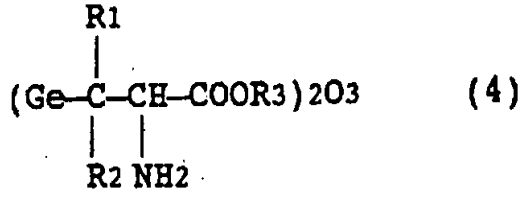
(1)

又は一般式2



(3)

又は一般式4



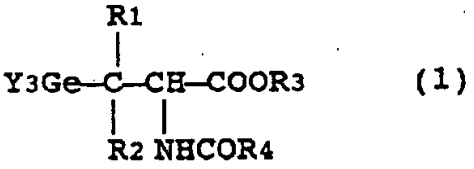
(4)

1

【特許請求の範囲】

【請求項1】　式

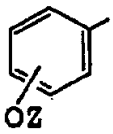
【化1】



(1)

（式中、Yはハロゲン原子又は水素原子を、R1及びR3は水素原子又は低級アルキル基を、R2は低級アルキル基、カルボキシアルキル基又は

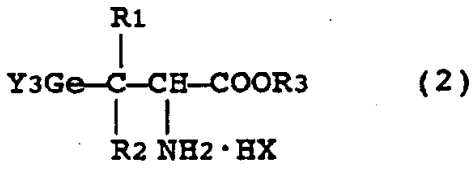
【化2】



（Zは水素原子又はアセチル基を表す）を、R4は低級アルキル基又はベンジルオキシ基をそれぞれ表わす）で表わされることを特徴とする有機ゲルマニウム化合物。

【請求項2】　式

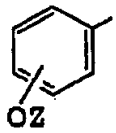
【化3】



(2)

（式中、Yはハロゲン原子又は水素原子を、R1及びR3は水素原子又は低級アルキル基を、R2は低級アルキル基、カルボキシアルキル基又は

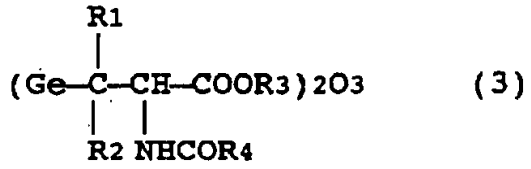
【化4】



（Zは水素原子又はアセチル基を表す）を、Xはハロゲン原子それぞれ表わす）で表わされることを特徴とする有機ゲルマニウム化合物。

【請求項 3】　式

【化5】

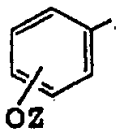


(3)

（式中、R1及びR3は水素原子又は低級アルキル基を、R2は低級アルキル基、カルボキシアルキル基又は

【化6】

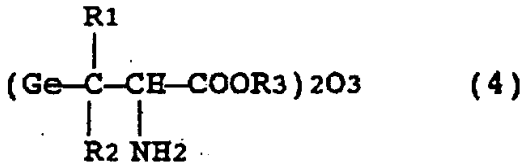
2



（Zは水素原子又はアセチル基を表す）を、R4は低級アルキル基又はベンジルオキシ基をそれぞれ表わす）で表わされることを特徴とする有機ゲルマニウム化合物。

【請求項4】　式

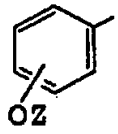
【化7】



(4)

（式中、R1及びR3は水素原子又は低級アルキル基を、R2は低級アルキル基、カルボキシアルキル基又は

【化8】



（Zは水素原子又はアセチル基を表す）をそれぞれ表わす）で表わされることを特徴とする有機ゲルマニウム化合物。

【発明の詳細な説明】

【０００１】

【産業上の利用分野】本発明は有機ゲルマニウム化合物に関するものである。

【０００２】

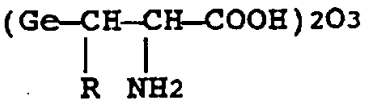
【従来の技術及び発明が解決しようとする課題】炭素の同族体であるゲルマニウムGeについては、近年になって、その有機化合物に関する研究やその結果の発表が活発に行なわれるようになるに従い、各方面、特に医学や薬学の分野からも注目されるようになっている。例えば、ゲルマニウムのプロピオン酸誘導体と酸素原子とが２：３の割合で結合した有機ゲルマニウム化合物であるカルボキシエチルゲルマニウムセスキオキサイド（特公昭４６－２４９８号）については、自然高血圧症ラットの血圧降下作用やアミロイド変化の軽減作用のみならず、マクロファージやNK細胞の活性化並にインターフェロン誘起作用や、抗腫瘍作用等を示すことが報告され、臨床的にも試用されている。

【０００３】而して、上記カルボキシエチルゲルマニウムセスキオキサイドは、基本的に、（Ｇｅ－ＣＨ2－ＣＨ2－ＣＯＯＨ）2Ｏ3なる化学式で表わされるものであるので、仮に上記化学式におけるカルボキシル基－ＣＯＯＨのα位にアミノ基を導入することができれば、このような化合物は、所謂アミノ酸の一種と考えることができる。

（NH2）COOHなる化学式で表わされる化合物の総称であって、生体の必須構成成分として、生命現象のみられる全ての生物界に存在するものであることは良く知られている。そして、アミノ酸の重要性は、アミノ酸が結合してタンパク質を形成する点のみならず、生体内においてアミノ酸は様々に代謝され、生体にとって重要な他の物質の前駆体となっている点にもあるのである。従って、すでに優れた薬理作用を示すことが知られている前記カルボキシエチルゲルマニウムセスキオキサイドに対し、その部分構造として、上記アミノ酸構造を導入できれば、この有機ゲルマニウム化合物が新たな有用性を示すものであることが充分に期待される。

【0005】一方、特開平02－62885号公報には、

【化9】

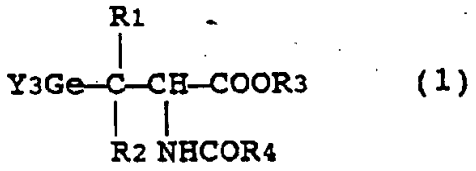


（Rは水素原子、低級アルキル基又はフェニル基を表す）等の側鎖にアミノ基を有する有機ゲルマニウム化合物が開示されているが、当該公報に実質的に開示されているアミノ酸構造を導入したもの以外の有機ゲルマニウム化合物を合成することができれば、それらの化合物が更に新たな有用性を示すものであることが期待される。

【0006】

【課題を解決するための手段】本発明は上述した従来技術に鑑みてなされたもので、本発明の第一の有機ゲルマニウム化合物は、式

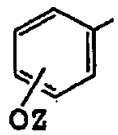
【化10】



（1）

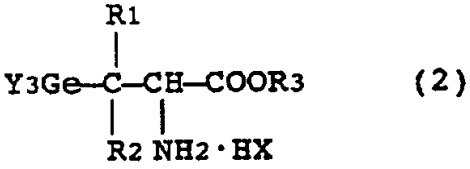
（式中、Yはハロゲン原子又は水素原子を、R1及びR3は水素原子又は低級アルキル基を、R2は低級アルキル基、カルボキシアルキル基又は

【化11】



（Zは水素原子又はアセチル基を表す）を、R4は低級アルキル基又はベンジルオキシ基をそれぞれ表わす）で表わされることを特徴とするものであり、本発明の第二の有機ゲルマニウム化合物は、式

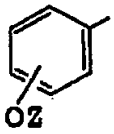
【化12】



（2）

（式中、Yはハロゲン原子又は水素原子を、R1及びR3は水素原子又は低級アルキル基を、R2は低級アルキル基、カルボキシアルキル基又は

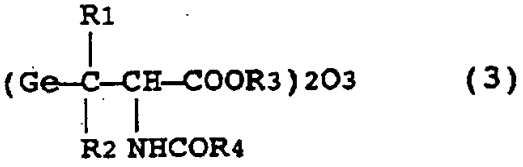
【化13】



（Zは水素原子又はアセチル基を表す）を、Xはハロゲン原子それぞれ表わす）で表わされることを特徴とするものである。

【0007】又、本発明の第三の有機ゲルマニウム化合物は、式

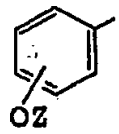
【化14】



（3）

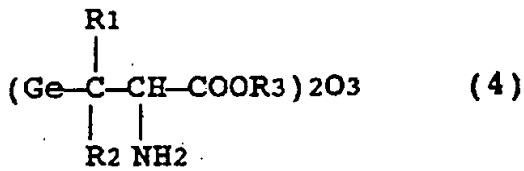
（式中、R1及びR3は水素原子又は低級アルキル基を、R2は低級アルキル基、カルボキシアルキル基又は

【化15】



（Zは水素原子又はアセチル基を表す）を、R4は低級アルキル基又はベンジルオキシ基をそれぞれ表わす）で表わされることを特徴とするものであり、更に、本発明の第四の有機ゲルマニウム化合物は、式

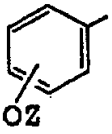
【化16】



（4）

（式中、R1及びR3は水素原子又は低級アルキル基を、R2は低級アルキル基、カルボキシアルキル基又は

【化17】



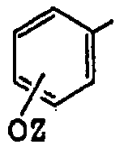
（Zは水素原子又はアセチル基を表す）をそれぞれ表わ

5

【0008】以下に本発明を詳細に説明する。

【0009】先ず、本発明の第1の有機ゲルマニウム化合物は、上記式（1）で表わされるものであって、ゲルマニウムのプロピオン酸誘導体を基本構造とし、ゲルマニウム原子には置換基Yが3つ結合すると共に、プロピオン酸構造におけるα位にはアセチル基やベンジルオキシカルボニル基等の保護基で保護されたアミノ基が、又、β位には二つの置換基R_1及びR_2が結合しており、更にプロピオン酸の酸素官能基はCOOR_3となっている。ここで、式（1）中のYはハロゲン原子又は水素原子を、R_1及びR_3は水素原子又はメチル基、エチル基、n－プロピル基、iso－プロピル基等の1乃至5程度の炭素で構成される低級アルキル基を、R_2はR_1と同様の低級アルキル基、カルボキシメチル基等のカルボキシアルキル基又は

【化18】



（Zは水素原子又はアセチル基を表す）をそれぞれ表わしている。

【0010】又、本発明の第二の有機ゲルマニウム化合物は、上記式（2）で表わされるものであり、上記式（1）で表わされる化合物において、アセチル基等の保護基により保護されていたアミノ基が、そのハロゲン化水素HX（Xはハロゲン原子を表わす）の塩となっている点を除いては、式（1）で表わされる化合物と同様である。

【0011】一方、本発明の第三の有機ゲルマニウム化合物は、式（3）で表わされるものであり、この化合物は、ゲルマニウムのプロピオン酸誘導体と酸素原子とが2：3の割合で結合したものである点で、上記式（1）及び式（2）で表わされる化合物と異なっているが、それ以外は基本的に式（1）で表わされる化合物と同様である。

【0012】尚、上記説明した式（1）、式（2）及び式（3）で表わされる化合物は、以下に説明する本発明の第四の有機ゲルマニウム化合物を合成する際の中間体として極めて有用性が高い。

【0013】而して、本発明の最終的な目的化合物は、上記式（4）で表わされるものであり、上記式（3）で表わされる化合物におけるアミノ基を保護していたアセチル基等の保護基が除去されたものに相当する。即ち、

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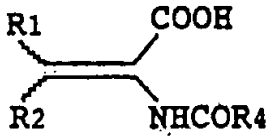
【0014】上記化合物（4）については、それが従来に存在しなかった構造のものであるので、新たな有用性を示すことが充分期待される。そこで、上記本発明の化合物の有用性を確認するため、食品成分であるアミノ化合物と還元糖との反応であって、食品の劣化の一因とされているメイラード反応の抑制効果を検討したところ、上記化合物（4）は、低濃度でメイラード反応を効果的に抑制したのである。

【0015】而して、上記説明した本発明の有機ゲルマニウム化合物は、次に説明するような製造方法により、製造することができる。

【0016】即ち、上記式（1）で表される本発明化合物のうち、置換基Yがハロゲン原子で置換基R_3が水素原子のものは、予め置換基R_1及びR_2を導入してある不飽和化合物

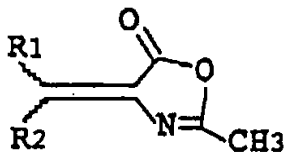
【化19】



に対し、式HGeY$_3$（式中、Yはハロゲン原子を表わす）で表わされるハロゲン化化合物を付加させればよいのである。尚、この反応は、エチルエーテル等の有機溶媒中又は塩酸等の無機溶媒中で進行する。

【0017】又、上記式（1）で表される本発明化合物のうち、置換基Yがハロゲンで置換基R_3が水素原子のものは、予め置換基R_1及びR_2を導入してあるアズラクトン体

【化20】



を加水分解して上記と同様の不飽和化合物とし（ただし、単離することは必須ではない）、この不飽和化合物に対し、式HGeY$_3$で表わされるハロゲン化化合物を付加させても得ることができる。

【0018】更に、上記式（1）で表される本発明化合物におけるGe－Y結合を、例えば水素化ほう素カリウムKBH_4で還元すれば、式（1）で表される本発明化合物のうち、置換基Yが水素原子のものとすることができ、例えばチオニルクロライドと低級アルコールとの反応物を作用させれば、式（1）で表される本発明化合物

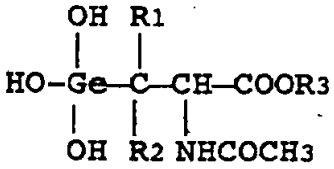
本発明第二の化合物とすることができるが、この反応は、上記式（１）で表わされる化合物を塩酸等のハロゲン化水素水溶液により扱えばよく、又、式（１）で表わされる化合物（但し、置換基Ｙが水素原子のものを除く）を加水分解反応に付すと、R_3の種類にかかわらず、上記式（３）で表わされる本発明第三の化合物とすることができる。

【００２０】尚、式（１）で表される本発明化合物のうち、置換基Ｙが水素原子のものは、これを適宜に酸化することによって、式（３）で表わされる本発明第三の化合物とすることができる。

【００２１】そして、上記式（２）で表わされる化合物（但し、置換基Ｙが水素原子のものを除く）を加水分解することにより、最終的に、上記式（４）で表わされる本発明第四の化合物と製造することができるのである。尚、式（４）で表わされる本発明第四の化合物は、式（１）又は式（３）で表される化合物より導くこともできる。

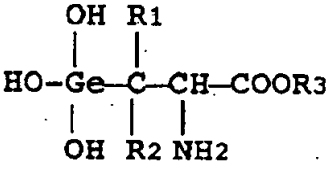
【００２２】而して、以上のようにして得られた本発明の化合物について測定したスペクトルデータは、本発明の化合物がいずれも上記の式で表されることを良く支持している。尚、上記式（３）及び（４）で表される本発明の化合物は、水中では、

【化２１】



又は

【化２２】



のような構造をとっているものである。

【００２３】

【実施例】以下に本発明を実施例により更に詳細に説明する。

【００２４】実施例１

式（１）で表される本発明化合物（但しR_3＝Ｈ）の合成

ａ）２－アセトアミドー３－メチルクロトン酸６．２８ｇ（０．０４ｍｏｌ）を６０ｍｌの濃塩酸中に加え、トリクロルゲルマン４．０１ｇ（０．０５ｍｏｌ）を加えた後、室温で６３時間撹拌した。析出した結晶を濾過して分取し、アセトン及びヘキサンから再結晶すると、２－アセトアミドー３－メチルー３－（トリクロルゲルミル）ブタン酸（式（１）において、Ｙ＝Ｃｌ、R_1

＝R_4＝CH_3の化合物）が９．６８ｇ（収率７１．８％）得られた。

融点：１５０℃（dec.）

Anal.Calcd.：C 24.94；H 3.59；N 4.15

Found　　：C 24.93；H 3.58；N 4.07

IR　ν　KBr/max　cm^{-1}：3330（N-H），1725（C=O），1605（C=O），405（Ge-Cl）

^{1}H-NMR（$CDCl_3$+CD_3OD）　δ：1.40（6H，s，C-(CH_3)$_2$），2.07（3H，s，CO-CH_3），5.00（1H，s，CH）

^{13}C-NMR（Aceton-d_6）　δ：19.65，21.42（($\underline{C}H_3$)$_2$），22.63（N-$\underline{C}O$-CH_3），51.29（Ge-$\underline{C}$），56.91（$\underline{C}H$），171.16，173.43（$\underline{C}OO$，$\underline{C}ON$ changable）

【００２５】ｂ）スレオニン１１．９ｇを、水酸化ナトリウム４．０ｇを含む水溶液に溶解し、氷冷しながら、無水酢酸１０．２ｇと水酸化ナトリウム４．０ｇを含む水溶を同時に加え、そのまま３時間撹拌した。反応終了後、希塩酸を１当量加え、エバポレーターで溶媒を留去して得られた無色のシロップにエタノールを加え、沈殿を濾別し、エタノール層を濃縮することにより、ほぼ定量的にＮ－アセチルスレオニンを無色のシロップとして得た。

【００２６】得られたＮ－アセチルスレオニンを大過剰の無水酢酸に溶解し、室温で１６時間撹拌することにより、アズラクトン体とした。反応終了後、沈殿を濾過し、濾液を少しずつ大量の水中に注ぐことによりアズラクトンを加水分解し、エバポレーターで溶媒を留去して、２－アセトアミノ－２－ブテン酸を定量的に黄色ガム状物質として得た。

【００２７】得られた２－アセトアミノ－２－ブテン酸４．３ｇをクロロホルムに溶解し、トリクロルゲルマン９．２ｇを加えた後、室温で１９時間撹拌した。反応終了後、溶媒を留去すると、２－アセトアミドー３－（トリクロルゲルミル）ブタン酸（式（１）において、Ｙ＝Ｃｌ、R_1＝R_4＝CH_3、R_2＝Ｈの化合物）を定量的に黄色シロップ状物質として得た。

^{1}H-NMR（CD_3OD）　δ：1.33，1.37（3H，各ｄ，CH_3），2.04(3H，s，CH_3CO)，2.5～2.9（1H，m，Ge-$\underline{C}$H），4.90，4.94（1H，各d，NOC-CH）

【００２８】ｃ）尚、式（１）で表される他の化合物も、上記ａ又はｂに記載した方法とほぼ同様の方法で得ることができた。得られた化合物の収率及び物性は以下及び表１に例示するとおりである。

【００２９】２－アセトアミドー３－（トリクロルゲルミル）ペンタン酸（式（１）において、Ｙ＝Ｃｌ、R_1＝Ｈ、R_2＝CH_2CH_3、R_4＝CH_3の化合物）

収率：７３．７％

融点：１６３～１６４℃

Anal.Calcd.：C 24.94；H 3.59；N 4.15

Found　　：C 24.81；H 3.52；N 4.20

IR　ν　KBr/max　cm^{-1}：3330（N-H），1730（C=O），164

9

0 (C=O), 430 (Ge-Cl)

^{1}H-NMR (Aceton-d$_6$) δ：1.17 (3H, t, CH$_3$), 1.86 (1H, ddq, CH$_3$-C-Ha),2.00 (1H, ddq, CH$_3$-C-Hb), 2.08 (3H, s, CO-CH$_3$),2.90 (1H, ddd, Ge-CH), 5.10 (1H, d, CH-CO)

^{13}C-NMR (Aceton-d$_6$) δ：13.32 (CH$_3$), 19.99 (CH$_2$), 22.31 (CO-CH$_3$), 52.66 (Ge-C), 53.32 (CH),171.59, 172.07 (COO, CON changable)

【００３０】２－アセトアミド－４－メチル－３－（トリクロルゲルミル）ペンタン酸（式（１）において、Y＝Cl、R$_1$＝H、R$_2$＝CH（CH$_3$）$_2$、R$_4$＝CH$_3$の化合物）

収率：６０．１％

融点：１１９～１２０℃

Anal.Calcd.：C 27.36；H 4.02；N 3.99

Found　　：C 27.39；H 4.01；N 3.99

IR ν KBr/max cm^{-1}：1720 (C=O), 1620 (C=O), 415 (Ge-Cl)

^{1}H-NMR (CDCl$_3$, CD$_3$OD) δ：1.19, 1.23 (3H×2, d, (CH$_3$)$_2$), 2.07 (3H, s, CO-CH$_3$),2.33 (1H, oct, (CH$_3$)$_2$-CH), 2.93 (1H, dd, Ge-CH), 5.16 (1H, d, CH-CO)

【００３１】２－アセトアミド－３－メチル－３－（トリクロルゲルミル）ペンタン酸（式（１）において、Y＝Cl、R$_1$＝CH$_3$、R$_2$＝CH$_2$CH$_3$、R$_4$＝CH$_3$の化合物）

収率：５９．４％（ジアステレオマーの混合物）

融点：１６３～１６４℃

Anal.Calcd.：C 27.36；H 4.02；N 3.99

Found　　：C 27.05；H 4.19；N 3.88

IR ν KBr/max cm^{-1}：3360(N-H), 1725, 1660 (C=O), 410, 395 (Ge-Cl)

^{1}H-NMR (CDCl$_3$+CD$_3$OD) δ：1.12, 1.17 (3H×2, t×2, Ge-C-C-CH$_3$),1.37, 1.42 (3H×2, s×2, Ge-C-CH$_3$), 1.89 (2H×2, q, Ge-C-CH$_2$),2.10 (3H×2, s, CO-CH$_3$), 5.18 (1H×2, s, CH-CO)

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＊【００３２】２－（カルボベンジルオキシアミノ）－３－（トリクロルゲルミル）ペンタン二酸（式（１）において、Y＝Cl、R$_1$＝H、R$_2$＝CH$_2$COOH、R$_4$＝OCH$_2$C$_6$H$_5$の化合物）

収率：７５．１％（ジアステレオマーの混合物）

融点：１２３℃（dec.）

IR ν KBr/max cm^{-1}：1708(C=O)

^{1}H-NMR (CD$_3$OD) δ：2.80～3.20 (3H, GeCH-CH$_2$), 4.87 (1H, CH-N), 5.21 (2H, CH$_2$-ph),7.44 (5H, pH)

^{13}C-NMR (CD$_3$OD) δ：31.35, 32.64 (Ge-CH$_2$-CH$_2$), 54.50, 55.27 (Ge-CH$_2$-CH),68.33 (CH$_2$-pH), 129.1, 129.3, 129.7 (pH)

【００３３】ｄ）２－アセトアミド－３－（トリクロルゲルミル）ブタン酸（式（１）において、Y＝Cl、R$_1$＝R$_4$＝CH$_3$、R$_2$＝Hの化合物）９．２ｇを水酸化カリウム水溶液に溶解し、ｐＨ７とした後、水素化ほう素カリウム５．６６ｇを加え、室温で３０分間撹拌した。反応終了後、希塩酸を加えてｐＨ１とし、沈殿を濾過し、濾液を酢酸エチルエステルで抽出した。酢酸エチルエステル層を無水硫酸マグネシウムで乾燥後、濃縮することにより、２－アセトアミド－３－ゲルミルブタン酸（式（１）においてY＝H、R$_1$＝R$_4$＝CH$_3$、R$_2$＝Hの化合物）を無色の粉状物質として４．７ｇ得た。

収率：７１．３％（ジアステレオマーの混合物）

融点：９９～１０５℃

Anal.Calcd.：C 32.79；H 5.96；N 6.37

Found　　：C 32.91；H 6.10；N 6.22

IR ν KBr/max cm^{-1}：2080 (GeH),1710 (CO), 1610 (C-N)

^{1}H-NMR (CD$_3$OD) δ：1.19, (3H, d, CH$_3$), 1.8～2.1 (1H,m,Ge-CH),1.97, 1.99 (3H, 各s, CH$_3$CO), 3.58, 3.61 (3H, 各d, GeH3),4.48, 4.57 (1H, 各d, CH-NAc)

【００３４】

【表１】

＊

Y	R$_1$	R$_2$	R$_3$	R$_4$	収率
Cl	CH_2CH_3	H	H	CH_3	73.7
Cl	$CH_2CH_2CH_3$	H	H	CH_3	77.0
Cl	H	p-OH-C_6H_5	H	CH_3	87.2
Cl	CH_3	CH_3	CH_2CH_3	CH_3	80

【００３５】実施例２

式（２）で表される本発明化合物（但しR$_3$＝H）の合成

ａ）２－アセトアミド－３－（トリクロルゲルミル）ペンタン酸（式（１）において、Y＝Cl、R$_1$＝H、R$_2$＝CH$_2$CH$_3$の化合物）１６．８６ｇ（０．０５ｍｏ

※２．５時間加熱還流した。溶媒を留去し、析出した結晶を１００ｍｌの水に溶解し、塩化水素ガスを約１時間（但し、発熱が停止するまで）流した。冷却後、析出した結晶を濾取することにより、２－アミノ－３－（トリクロルゲルミル）ペンタン酸塩酸塩（式（２）において、X＝Y＝Cl、R$_1$＝H、R$_2$＝CH$_2$CH$_3$の化合

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収率：６０．１％
融点：１８０～１８１℃(dec.)
Anal.Calcd.：C 18.11 ; H 3.34 ; N 4.22
Found　　：C 17.92 ; H 3.31 ; N 4.02
IR　ν　KBr/max　cm^{-1}：1750 (C=O), 420 (Ge-Cl)
^{1}H-NMR (CD$_3$OD)　δ：1.17 (3H, t, CH$_3$), 1.73, 1,94 (1H×2, m×2, CH$_3$-CH$_2$),2.62 (1H, m, Ge-CH), 4.56 (1H, br, CH-N)
^{13}C-NMR (CD$_3$OD)　δ：13.46 (CH$_3$), 18.85 (CH$_2$), 54.12 (CH-N)

【００３６】ｂ）尚、式（２）で表される他の化合物も、上記ａに記載した方法とほぼ同様の方法で得ることができた。得られた化合物の収率及び物性は以下及び表２に例示するとおりである。

【００３７】２－アミノ－４－メチル－３－（トリクロルゲルミル）ペンタン酸塩酸塩（式（２）において、Ｘ＝Ｙ＝Ｃｌ、Ｒ$_1$＝Ｈ、Ｒ$_2$＝ＣＨ（ＣＨ$_3$）$_2$の化合物）
収率：６１．０％
融点：１６５～１６６℃(dec.)
Anal.Calcd.：C 20.85 ; H 3.79 ; N 4.05
Found　　：C 20.80 ; H 3.90 ; N 4.35
IR　ν　KBr/max　cm^{-1}：1730 (C=O), 420 (Ge-Cl)
^{1}H-NMR (CD$_3$OD+CDCl$_3$)　δ：1.19, 1.29 (6H, d×2, (CH$_3$)$_2$), 2.47 (1H, oct, (CH$_3$)$_2$-CH),3.07 (1H, dd, Ge-CH), 4.60 (1H, d, CH-CO)
^{13}C-NMR (CD$_3$OD)　δ：21.02, 23.71 ((CH$_3$)$_2$), 27.63 ((CH$_3$)$_2$-CH), 50.86 (Ge-CH),53.48 (N-CH), 170.46 (CO)

【００３８】２－アミノ－３－メチル－３－（トリクロルゲルミル）ブタン酸塩酸塩（式（２）において、Ｘ＝Ｙ＝Ｃｌ、Ｒ$_1$＝Ｒ$_2$＝ＣＨ$_3$の化合物）

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＊収率：８８．１％
融点：１４９～１５０℃(dec.)
Anal.Calcd.：C 18.11 ; H 3.34 ; N 4.22
Found　　：C 18.12 ; H 3.20 ; N 4.56
IR　ν　KBr/max　cm^{-1}：1750 (C=O), 430, 405 (Ge-Cl)
^{1}H-NMR (CD$_3$OD+CDCl$_3$)　δ：1.44 (3H, s, CH$_3$), 1.65 (3H, s, CH$_3$), 4.42 (1H, s, CH-CO)

【００３９】２－アミノ－３－メチル－３－（トリクロルゲルミル）ペンタン酸塩酸塩（式（２）において、Ｘ＝Ｙ＝Ｃｌ、Ｒ$_1$＝ＣＨ$_3$、Ｒ$_2$＝ＣＨ$_2$ＣＨ$_3$の化合物）
収率：６１．０％（ジアステレオマーの混合物）
融点：１５０℃(dec.)
Anal.Calcd.：C 20.85 ; H 3.79 ; N 4.05
Found　　：C 20.55 ; H 3.98 ; N 4.47
IR　ν　KBr/max　cm^{-1}：1765 (C=O), 420, 400 (Ge-Cl)
^{1}H-NMR (CD$_3$OD)　δ：1.13 (3H×2, t, Ge-C-C-CH$_3$), 1.33, 1.57 (3H×2, s×2, Ge-C-CH$_3$),1.67～2.57 (2H×2, m, Ge-C-CH$_2$), 4.42, 4.52 (1H×2, s×2, CH-CO)

【００４０】２－アミノ－３－（トリクロルゲルミル）ペンタン二酸臭化水素酸塩（式（２）において、Ｘ＝Ｂｒ、Ｙ＝Ｃｌ、Ｒ$_1$＝Ｈ、Ｒ$_2$＝ＣＨ$_2$ＣＯＯＨの化合物）
融点：１５３℃(dec.)
IR　ν　KBr/max　cm^{-1}：1723 (C=O)
^{1}H-NMR (CD$_3$OD)　δ：2.80～3.10 (3H,Ge-CH-CH$_2$), 4.68, 4.78 (1H,CH-N)

【００４１】
【表２】

X	Y	R_1	R_2	R_3	収率
Cl	Cl	CH_2CH_3	H	H	60.1
Cl	Cl	$CH_2CH_2CH_3$	H	H	69.7
Cl	Cl	H	p-OH-C_6H_5	H	63.5
Cl	Cl	CH_3	CH_3	CH_2CH_3	66.3

【００４２】実施例３
式（３）で表される本発明化合物（但しＲ$_3$＝ＣＨ$_2$ＣＨ$_3$）の合成
ａ）２－アセトアミド－４－メチル－３－（トリクロルゲルミル）ペンタン酸（式（１）において、Ｙ＝Ｃｌ、Ｒ$_1$＝Ｈ、Ｒ$_2$＝ＣＨ（ＣＨ$_3$）$_2$、Ｒ$_3$＝Ｈ、Ｒ$_4$＝ＣＨ$_3$の化合物）１０．５３ｇ（０．０３ｍｏｌ）を５０ｍｌのエタノールに溶解し、チオニルクロライド３．９３ｇ（０．０３３ｍｏｌ）を加えて１時間加熱還流した。溶媒を留去すると結晶と油状物の混合物が得られるので、これをエーテルで洗浄し、不溶物を濾過して濾液を濃縮乾固すると、結晶と油状物の混合物が得られた。これを３００ｍｌの水に溶解して３時間撹拌し、不溶物を濾過※して濾液を陰イオン交換樹脂（ＩＲＡ－４５、ＡｃＯＨ）に通して脱塩素し、濾液を濃縮乾固することにより、１－（１－アセトアミド－１－エトキシカルボニルメチル）－２－メチルプロピルゲルマニウムセスキオキサイド（式（３）において、Ｒ$_1$＝Ｈ、Ｒ$_2$＝ＣＨ（ＣＨ$_3$）$_2$、Ｒ$_4$＝ＣＨ$_3$の化合物）を、微黄色の粉末として４．０２ｇ得た。
収率：５６．５％
融点：１６０℃(dec.)
Anal.Calcd.：C 40.46 ; H 6.11 ; N 4.72
Found　　：C 40.18 ; H 5.93 ; N 4.51
IR　ν　KBr/max　cm^{-1}：1735, 1660 (C=O), 875 (Ge-O)

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^{1}H-NMR (D_2O) δ：1.05 (6H, m, $(CH_3)_2$), 1.28 (3H, t, O-C-CH_3), 2.06 (3H, s, CO-CH_3),2.07 (1H, m, $(CH_3)_2$-CH), 2.11 (1H, m, Ge-CH), 4.23 (2H, m, O-CH_2),4.97 (1H, d, CH-CO)

【００４３】ｂ）尚、式（３）で表される他の化合物も、上記ａに記載した方法とほぼ同様の方法で得ることができた。得られた化合物の収率及び物性は以下及び表３に例示するとおりである。

【００４４】２－アセトアミドー２－（エトキシカルボニル）－１，１－ジメチルーエチルゲルマニウムセスキオキサイド（式（３）において、R_1＝R_2＝R_4＝CH_3の化合物）

収率：５９．３％

融点：１７０℃(dec.)

Anal.Calcd.：C 38.22；H 5.70；N 4.95

Found　　：C 37.99；H 5.61；N 4.79

IR ν KBr/max cm^{-1}：1735, 1660 (C=O), 860 (Ge-O)

^{1}H-NMR (D_2O) δ：1.22, 1.25 (3H×2, s×2, Ge-C-$(CH_3)_2$), 1.30 (3H, t, CH_2-CH_3),2.11 (3H, s, CO-CH_3), 4.27(2H, br, CH_2), 4.80 (1H, s, CO-CH)

【００４５】１－（１－アセトアミドー１－エトキシカルボニルメチル）－１－メチルプロピルゲルマニウムセスキオキサイド（式（３）において、R_1＝R_4＝CH_3、R_2＝CH_2CH_3の化合物）

収率：３２．２％（ジアステレオマーの混合物）

融点：１７５℃(dec.)

Anal.Calcd.：C40.46；H 6.11；N 4.72

Found　　：C40.21；H 5.92；N 4.55

IR ν KBr/max cm^{-1}：1730, 1660 (C=O), 860 (Ge-O)

^{1}H-NMR (CH_3OD)：1.08 (3H×2, br, Ge-C-C-CH_3),1.28 (6H×2, br, Ge-C-CH_3, O-C-CH_3),1.73 (2H×2, br, Ge-C-CH_2), 2.04 (3H×2, br, CO-CH_3),4.19 (2H×2, br, O-CH_2), 4.86 (1H×2, br, CO-CH)

【００４６】

【表３】

R_1	R_2	R_3	R_4	収率
CH_2CH_3	H	CH_2CH_3	CH_3	57.0
$CH_2CH_2CH_3$	H	CH_2CH_3	CH_3	61.3
H	CH_2COOH	CH_2CH_3	CH_3	58.2
H	p-OH-C_6H_5	CH_2CH_3	CH_3	60.9

【００４７】実施例４

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で３０分間撹拌した。反応終了後、析出した沈殿を濾取し、エーテルで洗浄することにより、１－（１－アセトアミドー１－カルボキシメチル）エチルゲルマニウムセスキオキサイド（式（３）において、R_1＝H、R_2＝R_4＝CH_3の化合物）を無色の粉末として１．０ｇ得た。

収率：６０．１％（ジアステレオマーの混合物）

融点：２５７℃(dec.)

Anal.Calcd.：C 38.22；H 5.70；N 4.95

Found　　：C 38.13；H 5.52；N 4.01

IR ν KBr/max cm^{-1}：3700～2900 (NH, OH), 1720, 1650 (C=O), 880, 820 (Ge-O)

^{1}H-NMR (D_2O) δ：

ジアステレオマーａ 1.15 (3H, d, CH_3), 2.07 (3H, s, CH_3-CO),2.26 (1H, dq, Ge-CH), 4.82 (1H, d, N-CH)

ジアステレオマーｂ 1.26 (3H, d, CH_3), 2.06 (3H, s, CH_3-CO),2.22 (1H, dq, Ge-CH), 4.44 (1H, d, N-CH)

【００４８】ｂ）２－アセトアミドー３－（パラアセトキシフェニル）－３－トリクロルゲルミルプロパン酸（式（１）において、Y＝Ｃｌ、R_1＝H、R_2＝パラアセトキシフェニル、R_3＝H、R_4＝CH_3の化合物）１．８８ｇを水に溶解し、炭酸水素ナトリウム１．７８ｇを加え、室温で２０時間撹拌した後、１Ｎの水酸化ナトリウム水溶液４．４ｍｌを加え、更に２時間撹拌した。反応終了後、希塩酸を加えてｐＨ７とし、メタノールを加えて濾過した。濾過液を濃縮し、残渣にメタノールを加え、析出した沈殿を濾取する操作を２回行い、０．８２ｇの黄色粉末を得た。これを蒸留水に溶解し、陽イオン交換樹脂アンバーライトＩＲ１２０Ｂ（商品名）［H+型］と一晩撹拌後、水層を濃縮することにより、２－アセトアミドー２－カルボキシー１－パラハイドロキシフェニルエチルゲルマニウムセスキオキサイド（式（３）において、R_1＝H、R_2＝パラハイドロキシフェニル、R_4＝CH_3の化合物）を微黄色の粉末として７００ｍｇ得た。

収率：５８．９％（ジアステレオマーの混合物）

融点：３００℃＜(dec.)

Anal.Calcd.：C 38.22；H 5.70；N 4.95

Found　　：C 38.00；H 5.51；N 4.72

IR ν KBr/max cm^{-1}：3600～2500 (NH, OH), 1710, 1640 (C=O), 875, 840 (Ge-O)

^{1}H-NMR (D_2O) δ：1.87 (3H, s, CH_3-CO), 3.55 (1H, d, Ge-CH), 4.98 (1H, d, N-CH),6.87 (2H, d, OHのオ

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に懸濁し、水酸化ナトリウム0．44g（0．011mol）を加えて17時間攪拌した。反応終了後、濾過し、濾液を陽イオン交換樹脂アンバーライトIR120B（商品名）［H+型］に通して脱ナトリウムした後、濾液を濃縮乾固することにより、1－（1－アセトアミド－1－カルボキシメチル）－2－メチルプロピルゲルマニウムセスキオキサイド（式（3）において、R_1=H、R_2=CH（CH_3）2、R_4=CH_3の化合物）を微黄色の粉末として1．36g得た。

収率：50．6％

融点：207℃(dec.)Anal.Calcd.：C35.75；H5.25；N5.21

Found　　：C35.56；H5.06；N5.20

IR ν KBr/max cm^{-1}：1740, 1665 (C=O), 875(Ge-O)

^{1}H-NMR (D_2O+NaOD) δ：1.06, 1.08 (6H, d, (CH_3)2), 2.06 (3H, s, CO-CH_3),1.83～2.33 (2H, m, CH-CH), 4.56 (1H, d, CO-CH)

【0050】d）尚、式（3）で表される他の化合物も、上記a、b又はcに記載した方法とほぼ同様の方法で得ることができた。得られた化合物の収率及び物性は以下及び表4に例示するとおりである。

【0051】2－アセトアミド－2－カルボキシ－1，1－ジメチルエチルゲルマニウムセスキオキサイド（式（3）において、R_1=R_2=CH_3、R_4=CH_3の化合物）

収率：82．5％

融点：210℃(dec.)

Anal.Calcd.：C33.00；H 4.75；N5.50

Found　　：C32.71；H 4.61；N 5.27

IR ν KBr/max cm^{-1}：1720, 1650 (C=O), 880(Ge-O)

^{1}H-NMR (D_2O) δ：1.08 (3H, s, CH_3), 1.17 (3H, s,*

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* CH_3), 2.11(3H, s, CO-CH_3),4.62 (1H, s, CO-CH)

^{13}C-NMR (D_2O, NaOD) δ：22.64, 23.71 ((CH_3)2), 24.98 (CO-CH_3), 38.54 (Ge-C), 64.28 (CH),176.68, 180.06 (COO,CON changable)

【0052】1－（1－アセトアミド－1－カルボキシメチル）－1－メチルプロピルゲルマニウムセスキオキサイド（式（3）において、R_1=CH_3、R_2=CH_2CH_3、R_4=CH_3の化合物）

収率：71．7％(ジアステレオマーの混合物)

融点：184℃(dec.)

Anal.Calcd.：C35.75；H5.25；N5.21

Found　　：C35.63；H5.19；N 5.19

IR ν KBr/max cm^{-1}：1720, 1660 (C=O), 870(Ge-O)

^{1}H-NMR (D_2O+NaOD) δ：ジアステレオマーa 1.01(3H, t, CH_3), 1.36 (1H, dq, CH_3-CHa),1.67 (1H dq, CH_3-CHb), 1.09 (3H, s, Ge-C-CH_3),2.10 (3H, s, CO-CH_3), 4.82 (1H, s, CO-CH)

ジアステレオマーb 0.99 (3H, t, CH_3), 1.50 (2H, dq, CH_3-CH_2),1.15 (3H, s, Ge-C-CH_3),2.10 (3H, s, CO-CH_3), 4.65 (1H, s, CO-CH)

^{13}C-NMR (D_2O, NaOD) δ：ジアステレオマーa 13.24 (Ge-C-CH_3), 20.73 (CH_3), 24.78 (CO-CH_3),30.77 (CH_2), 46.90 (Ge-C), 58.61 (CH-CO)

ジアステレオマーb 12.96 (Ge-C-CH_3), 21.36 (CH_3), 24.83 (CO-CH_3),27.94 (CH_2), 47.33 (Ge-C), 62.41 (CH-CO)

a、b　　177.10, 177.13, 180.19, 180.67 (COO,CON changable)

【0053】

【表4】

R_1	R_2	R_3	R_4	収率
CH_2CH_3	H	H	CH_3	96.9
$CH_2CH_2CH_3$	H	H	CH_3	78.2
H	CH_2COOH	H	CH_3	83.1

【0054】実施例5

式（4）で表される本発明化合物（但しR_3=H）の合成

a）2－アミノ－3－（トリクロロゲルミル）－ペンタン酸塩酸塩（式（2）において、X=Y=Cl、R_1=H、R_2=CH_2CH_3の化合物）8．29g（0．025mol）を100mlの水に溶解し、陽イオン交換樹脂アンバーライトIR120B（商品名）［H+型］に吸着させて水洗した後に2Nのアンモニア水で溶出し、

※化合物）を微黄色の粉末として4．62g得た。

収率：86．9％

融点：206℃(dec.)

Anal.Calcd.：C 28.23；H 4.74；N 6.5

Found　　：C 28.06；H 4.59；N 6.44

IR ν KBr/max cm^{-1}：1630(C=O), 870(Ge-O)

^{1}H-NMR (D_2O) δ：1.09 (3H, t, CH_3), 1.51(1H, ddq, CH_3-CHa), 1.74 (1H, ddq, CH_3-CHb),2.09 (1H, ddd, Ge-CH), 4.19 (1H, d, CO-CH)

キシフェニル）－３－トリクロルゲルミルプロパン酸（式（１）において、Ｙ＝Ｃｌ、R_1＝Ｈ、R_2＝パラアセトキシフェニル、R_4＝CH_3の化合物）９６９ｍｇに濃塩酸を加え、室温で２日間攪拌した。反応終了後、内容物を多量の水中に注ぎ不純物を濾過した。濾液を濃縮して得た残渣を蒸留水に溶解し、陽イオン交換樹脂アンバーライトＩＲ１２０Ｂ（商品名）［H+型］に吸着させ、５％アンモニア水で溶出し、溶出液を濃縮することにより、２－アミノ－２－カルボキシ－１－パラハイドロキシフェニルエチルゲルマニウムセスキオキサイド（式（４）において、R_1＝Ｈ、R_2＝パラハイドロキシフェニルの化合物）を微黄色の粉末として２００ｍｇ得た。

収率：４６．２％（ジアステレオマーの混合物）

融点：３００℃>(dec.)

Anal.Calcd.：C 28.23；H 4.74；N 6.5

Found　　：C 28.00；H 4.56；N 6.32

IR　ν　KBr/max　cm^{-1}：3700～2200 (NH_3+)，1630 (NH_3+)，1605 (C=O)，885，845 (Ge-O)

^{1}H-NMR　(D_2O)　δ：3.38 (1H，d，Ge-C<u>H</u>)，4.33 (1H，d，CO-C<u>H</u>)，6.87 (2H，d，OHのオルト位)，7.14 (2H，d，OHのメタ位)

【００５６】ｃ）１－（１－アセトアミド－１－カルボキシメチル）エチルゲルマニウムセスキオキサイド（式（３）において、R_1＝Ｈ、R_2＝CH_3、R_4＝CH_3の化合物）２００ｍｇを水に溶解し、更に濃塩酸０．２ｍｌを加え、１８時間加熱還流した。反応終了後、反応液を濃縮し、得られた白色結晶を水に再度溶解して不純物を濾過し、濾液を陽イオン交換樹脂アンバーライトＩＲ１２０Ｂ（商品名）［H+型］に通した。十分に水洗をした後、５．６％アンモニア水で溶出し、溶出液を濃縮することにより、１－（１－アミノ－１－カルボキシメチル）エチルゲルマニウムセスキオキサイド（式（４）において、R_1＝Ｈ、R_2＝CH_3の化合物）をオフホワイトの粉末として１２６ｍｇ得た。

収率：７６．３％

融点：２７０℃(dec.)

Anal.Calcd.：C 24.18；H 4.06；N 7.05

Found　　：C 24.00；H 3.88；N 6.91

IR　ν　KBr/max　cm^{-1}：3800～2500 (NH，OH)，1610 (C=O)，840，790(Ge-O)

^{1}H-NMR　(D_2O)　δ：

ジアステレオマーａ　1.19 (3H，t，CH_3)，2.19 (1H，dq，Ge-C<u>H</u>)，4.19 (1H d，CO-C<u>H</u>)

ジアステレオマーｂ　1.36 (3H，t，CH_3)，2.09 (1H，dq，Ge-C<u>H</u>)，3.86 (1H d，CO-C<u>H</u>)

【００５７】ｄ）尚、式（４）で表される他の化合物も、上記ａ、ｂ又はｃに記載した方法とほぼ同様の方法で得ることができた。得られた化合物の収率及び物性は以下及び表５に例示するとおりである。

【００５８】１－（１－アミノ－１－カルボキシメチル）－２－メチルプロピルゲルマニウムセスキオキサイド（式（４）において、R_1＝Ｈ、R_2＝$CH(CH_3)_2$の化合物）

収率：７１．０％

融点：１９１℃(dec.)

Anal.Calcd.：C 31.78；H 5.33；N 6.18

Found　　：C 31.48；H 5.09；N 6.10

IR　ν　KBr/max　cm^{-1}：1630 (C=O)，860 (Ge-O)

^{1}H-NMR　(D_2O)　δ：1.01，1.15 (6H，d，$(CH_3)_2$)，2.17 (1H，d sept，$(CH_3)_2$-C<u>H</u>)，2.29 (1H，dd，Ge-C<u>H</u>)，4.18(1H，d，C<u>H</u>-CO)

^{13}C-NMR　(D_2O)　δ：22.71，25.84 ($(\underline{C}H_3)_2$)，27.80 ($(CH_3)_2$-<u>C</u>H)，46.03 (Ge-<u>C</u>H)，56.89 (<u>C</u>H-N)，177.13 (<u>C</u>O)

【００５９】１－（１－アミノ－１－カルボキシメチル）－１－メチル－エチルゲルマニウムセスキオキサイド（式（４）において、R_1＝R_2＝CH_3の化合物）

収率：８０．０％

融点：１９０℃(dec.)

Anal.Calcd.：C 28.23；H 4.74；N 6.58

Found　　：C 28.04；H 4.64；N 6.56

IR　ν　KBr/max　cm^{-1}：1640(C=O)，850(Ge-O)

^{1}H-NMR　(D_2O)　δ：1.53 (3H，s，CH_3)，1.36 (3H，s，CH_3)，3.95 (1H，s，C<u>H</u>)

【００６０】１－（１－アミノ－１－カルボキシメチル）－１－メチル－プロピルゲルマニウムセスキオキサイド（式（４）において、R_1＝CH_3、R_2＝CH_2CH_3の化合物）

収率：８４．６％（ジアステレオマーの混合物）

融点：１９５℃(dec.)

Anal.Calcd.：C 31.78；H 5.33；N 6.18

Found　　：C 31.53；H 5.44；N 6.11

IR　ν　KBr/max　cm^{-1}：1650 (C=O)，845 (Ge-O)

^{1}H-NMR　(D_2O)　δ：1.06 (3H×2，t，Ge-C-C-CH_3)，1.17，1.38 (3H×2，s×2，Ge-C-CH_3)，1.30～2.27 (2H×2，m，Ge-C-CH_2)，4.00，4.19 (1H×2，s×2，CO-C<u>H</u>)

【００６１】２－アミノ－２－カルボキシ－１－（カルボキシメチル）エチルゲルマニウムセスキオキサイド（式（４）において、R_1＝Ｈ、R_2＝CH_2COOHの化合物）

収率：７４．２１％（ジアステレオマーの混合物）

融点：３４５℃(dec.)

IR　ν　KBr/max　cm^{-1}：1663 (C=O)

^{1}H-NMR　(D_2O)　δ：2.33 ～2.85 (3H，Ge-C<u>H</u>-CH_3)，4.10 (1H，C<u>H</u>-N)

^{13}C-NMR　(D_2O，dioxane)　δ：31.22，31.44 (Ge-CH_2-<u>C</u>H_2)，34.29，34.56 (ge-<u>C</u>H)，52.16，57.19(<u>C</u>H-N)，174.2，179.7 (C=O)

【００６２】

【表5】

R_1	R_2	R_3	収率
CH_2CH_3	H	H	86.9
$CH_2CH_2CH_3$	H	H	80.5
H	CH_3	CH_2CH_3	81.3
CH_3	CH_3	CH_2CH_3	84.2

【0063】

【参考実験】本発明化合物によるメイラード反応の阻害効果

1．試料溶液の調製

原液

Nα－t－Boc－L－Lysine(50mM)、グルコース(1M)を50mlの燐酸緩衝液240mlに溶解して原液とした。

コントロール液

原液30mlに50mlの燐酸緩衝液30mlに溶解してコントロール液とした。

＊有機ゲルマニウム化合物液

有機ゲルマニウム化合物のそれぞれ20mMをとり、50mMの燐酸緩衝液に溶解して50mlとし、そのうちの30mlを原液30mlと混合し、10mMの有機ゲルマニウム化合物液とした。

【0064】2．阻害効果の試験及び結果

上記各試料溶液を混合し、40℃の振盪条件下でインキュベートし、4、8、11日目にそれぞれから試料を採取し、297nm（極大吸収）における吸光度を測定した。結果を以下の表6に示す。

【表6】

化合物			吸光度(297nm)		
R_1	R_2	R_3	4日目	8日目	11日目
H	CH_2CH_3	H	0.37	0.54	1.35
H	p-OH-C_6H_5	H	0.34	0.53	1.31
H	CH_3	H	0.39	0.55	1.26
H	$CH(CH_3)_2$	H	0.33	0.55	1.30
CH_3	CH_3	H	0.33	0.51	1.25
CH_3	CH_2CH_3	H	0.32	0.52	1.21
H	CH_2COOH	H	0.31	0.55	1.19
CH_2CH_3	H	H	0.33	0.53	1.15
H	CH_3	CH_2CH_3	0.30	0.47	1.08
CH_3	CH_3	CH_2CH_3	0.29	0.48	1.05
H	H	H	0.39	1.17	2.78
C_6H_5	H	H	0.41	1.26	2.55
コントロール			0.50	1.51	3.13